A STUDY OF VIRAL INFECTIONS IN RENAL TRANSPLANT RECIPIENTS - RISK FACTORS, CLINICAL PROFILE AND OUTCOME ANALYSIS

Dissertation submitted in partial fulfilment of

the requirements for the degree of

D.M. (NEPHROLOGY)

BRANCH – III

DEPARTMENT OF NEPHROLOGY,

MADRAS MEDICAL COLLEGE,

CHENNAI – 600 003.

THE TAMIL NADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

AUGUST 2013

CERTIFICATE

This is to certify that this Dissertation entitled "**A STUDY OF VIRAL INFECTIONS IN RENAL TRANSPLANT RECIPIENTS –RISK FACTORS, CLINICAL PROFILE AND OUTCOME ANALYSIS**" is the bonafide original work of **Dr.R.ARUL**, in partial fulfillment of the requirement for D.M., (Nephrology) examination of the Tamilnadu Dr.M.G.R Medical University will be held in August 2013.

DR. N.GOPALAKRISHNAN MD D.M. FRCP,
Professor and Head
Department of Nephrology
Madras Medical College,
Chennai - 3

Prof. V. KANAGASABAI, M.D.,
Dean,
Madras Medical College,
Chennai – 3

.

DECLARATION

I, Dr.R.ARUL , solemnly declare that the dissertation titled "**A STUDY OF VIRAL INFECTIONS IN RENAL TRANSPLANT RECIPIENTS –RISK FACTORS, CLINICAL PROFILE AND OUTCOME ANALYSIS**" is the bonafide work done by me at Department of Nephrology, Madras Medical College under the expert guidance and supervision of **Dr.N.GOPALAKRISHNAN D.M, FRCP,** Professor of Nephrology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of D.M. Degree (Branch III) in Nephrology.

Place: Chennai Dr.R.ARUL

Date:

ACKNOWLEDGEMENT

I wish to express my sincere thanks to my most respected Chief **Prof.Dr.N.Gopalakrishnan D.M., FRCP,** Professor and Head, Department of Nephrology, Madras Medical College, Chennai for the constant guidance he rendered throughout the study.

I thank the **Dean**, Madras Medical College for permitting me to conduct this study at the Nephrology Department.

I owe my sincere thanks to Associate Professor of Nephrology **Dr. T.Balasubramanian D.M.,** for his guidance and advice throughout the study.

I am immensely grateful to **Dr. N. Malathy, Dr. M Haris, Dr. N.D. Srinivasa Prasad and Dr. R. Sakthirajan,** Assistant Professors of Nephrology for their valuable suggestions which helped me to model this study.

I extend my gratitude to **Dr Anila Abraham M.D.,** Consultant Nephropathologist for providing me the valuable resource for my study.

I am thankful to all my Colleagues, Technicians and Staff of the Department of Nephrology and Pathology and Microbiology Department, Madras Medical College, Chennai for all their help and support they extended for the successful completion of this dissertation.

My family and friends have stood by me during my times of need. Their help and support have been invaluable to the study.

My patients, who form the most integral part of the work, were always kind and cooperative. I cannot but pray for their speedy recovery and place this study as a tribute to them and to numerous others likely affected.

Above all I thank the Lord Almighty for His kindness and benevolence.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. R. Arul
PG in DM Nephrology
Madras Medical College, Chennai -3

Dear Dr. R. Arul

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " A study of viral infections in renal transplant recipients- risk factors, clinical profile and outcome analysis" No. 18012012.

The following members of Ethics Committee were present in the meeting held on 27.01.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan. MD	-- Chairperson
2	Prof. Pregna B. Dolia MD Vice Principal, Madras Medical College, Chennai -3 (Director , Institute of Biochemistry, MMC, Ch-3)	-- Member Secretary
3.	Prof. B. Kalaiselvi. MD Prof of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. Shruti Kamal MS Prof of Surgery, Madras Medical College , Ch-3	-- Member
5.	Thiru. S. Govindsamy. BA BL	-- Lawyer

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

CONTENTS

GLOSSARY

CMV	-	cytomegalovirus
UTI	-	urinary tract infection
EBV	-	Ebstein barr virus
HBV	-	Hepatitis B virus
HCV	-	hepatitis C virus
HIV	-	human immunodeficiency virus
HHV	-	Human herpes virus
HPV	-	Human papilloma virus
PTLD	-	Post transplant lymphoproliferative disorder
HSV	-	Herpes simplex virus
BKVN	-	BK virus associated nephropathy
BAL	-	Bronchoalveolar lavage
PCR	-	Polymerase chain reaction
TAC	-	tacrolimus
MMF	-	Mycophenolate mofetil
PDN	-	Prednisolone
AZA	-	azathioprine
CYC	-	cyclosporine
CNI	-	calcineurin inhibitor
GDF	-	graft dysfunction
DGF	-	delayed graft function
ATN	-	acute tubular necrosis
NODAT	-	New onset of diabetes mellitus
ART	-	Antirejection therapy
IFN	-	Interferon
no.	-	Number

INTRODUCTION

Renal transplantation has become the most effective means of rehabilitating patients with end stage renal disease. In well established centres , 90% 1 year graft survival and 95% patient survival is achieved. Inspite of this, infection occurs more than 60% of renal transplant recipients and being the one of the main cause of death in renal transplant recipients.

The factors give a challenge to the clinician for preventing the infection are:[1]

(a) Combination of lifelong immunosuppressive therapy

(b) Potential source of infection –endogenous and environmental and allograft itself

Risk of infections in transplant recipients[2]

(a) The occurrence of technical / anatomical mishaps that result in devitalized tissue, fluid collections , prolonged keeping of drains, catheter, endotracheal tubes, vascular access devices which compromise the barrier.

(b) The epidemiological exposure of the patient encounters divided into those occur in the community and another is those occurring in the hospital and donor derived and recipient derived exposures.

(c) individuals net state of immunosuppression

The interaction between the net state of immunosuppression and the environmental exposure should be a semiquantitative one. If the net state of immunosuppression is

minimal then an overwhelming exposure only cause the disease . Conversely if the net state of immunosuppression is high , the even minimal exposure will cause the disease.

Renal transplant recipients are susceptible to infections by different organisms. Impaired inflammatory responses due to immunosuppressive therapies hide the clinical and radiological findings affected by microbial infection. As a result ,evaluation and diagnosis is delayed. Specific microbiologic diagnosis is essential both for optimization of antimicrobial therapy and to avoid unnecessary drug toxicities. Routine antimicrobiologic prophylaxis is aimed at common infection i.e that includes trimethoprim-sulphamethoxazole (toxoplasmosis , pneumocystis, Nocardia, UTI) and valganciclovir(CMV and herpes groups) and antifungal (Kidney-pancreas transplantation)

In this study , we have been made to analyse the risk facors and clinical profile and outcome of viral infection in renal transplant recipient.

AIMS AND OBJECTIVES

1. To study the clinical profile of viral infections in renal transplant recipients.
2. To study the risk factors for viral infections and the effect of viral infections on graft outcome.

REVIEW OF LITERATURE

Immunosuppression make the recipient susceptible to many viral pathogens either due to community exposure (adeno,influenza) or commonly transmitted with allograft (CMV, EBV) or as a result of more distant exposure due to more immunosuppression (Chickenpox and varicella zoster)[3]. Mutilple simultaneous infections either two viral or viral and nonviral infections are also common.

Effects of viral infection:

It is divided into effects of invasive viral infection or form effects mediated by inflammatory responses or by alteration of host immune and inflammatory response. Direct effects due to tissue invasion and indirect effects due to release of cytokines causing immunomodulation[4] and further immunosuppression and producing more infections and also alter the expression of surface antigens provoking graft rejection. Infection with one virus stimulate the replication of other virus. Viral replication can also lead to production of cross reactive T cells directed against shared antigen between virus and the graft. .

The specific terms latency and reactivation is important in any transplant recipients. Many viral infections after transplantation result from the reactivation of latent viral infection in the host or from allograft. Latency and reactivation is noted in herpes group of viruses. Viral latency is characterized by due to low level or absence of detectable viral antigens and minimal transcription of productive or lytic cycle genes and expression of

latency associated viral transcripts[5]. Viral latency interrupted periodically, leads to reactivation of infectious virus.

CMV is latently present in CD14 monocytes and CD34 progenitor cells. EBV is latently present in lymphocytes.

Risk factors of viral infection after transplantation:

The risk is depend upon the variety of factors such as the intensity , virulence and the immunosuppressive regimen and the presence of preexisting antiviral immunity and the viral exposure mechanism. Steroids (reactivate HBV and HCV) and induction of T cell depleting antibodies (activate Herpes and HIV) , Tacrolimus (BK Virus),ATG (CMV), MMF(late CMV, Herpes zoster) and costimulatory blockade alters the susceptibility to viral infection .

Time pattern of viral infection:

Patients with history of herpes simplex infection present within 1 or 2 months after transplantation. Infections acquired from the donor such as HBV , HCV or HIV appear in the in the first month of transplantation. Earlier onset of hemophagocytic syndrome[6] due to EBV, CMV, VZV, HIV, HHV8, Parvovirus ,measles occur just after the transplantation. CMV both reactivation and new disease acquired in the peritransplant period appear in months 1to 4 or after cessation of prophylaxis .CMV retinitis and colitis occur later (6 to 12 months or later). BK virus nephropathy half occur in the first six month after transplantation and other half in the later period. Influenza and adeno and RSV and entero and para influenza can appear at any time. HHV6 and 7 can appear in the earlier months and HHV 8 occur in the later time period.

EBV infection and PTLD can occur within one year. In Hepatitis B and Hepatitis C infection, previously positive reactivation occur in earlier months and acquisition of new infection reactivation occur in later months. Individual risk factors must be considered for evaluation of skin and anogenital lesion caused by papilloma virus. Herpes simplex virus infection reactivate at the earlier months of transplantation.

CYTOMEGALOVIRUS INFECTION:

CMV is the the significant cause of morbidity and mortality among transplant recipients. Human CMV or human Herpes virus 5 is the largest known human virus. It is double stranded DNA virus and icosahedral in shape and consists of inner core and a capsid and an envelope. White blood cells, CD13+ve cells are in particular are the reservoir of CMV.

CMV replication produces the immediate early, early, and late antigens. The early antigen gene products direct viral DNA synthesis. The three common drugs used in CMV infection act by interrupting the DNA synthesis. Late antigens appear after DNA synthesis and monitoring the late antigen level may be more relevant when assessing the response to therapy.

CMV has the capability to alter the expression of MHC class I molecules which may allow the evasion of recognition by cytotoxic T cells , but make infected T cells vulnerable to NK cell attack and directed the production of viral IL- 10 blocks proinflammatory cytokine synthesis and suppress the ability of macrophages to serve as antigen presenting cells.

After the primary infection, the virus establishes the latency within host. TNF alpha (induced by allogenic response after transplantation, anti thymocyte globulin and sepsis

induce ie gene expression through activation of major ie promoter enhancer which reactivates latent CMV[7].

Risk factor and pathogenesis:

CMV infection occurs within 1-4months of transplantation. Symptomatic CMV infection occurs in 20-60% of all transplant recipients. In CMC vellore, seropositivity in our population is about 98%. The prevalence of clinical CMV disease in post transplant 30%consistent with reinfection and reactivation.

The Major risk factors responsible are the nature and dose of immunosuppressive medication, MMF >3g/day. Sirolimus seems to have a protective role. Induction with depleting agent directly activate viral infection. Recipient / Donor serology status, immunosuppressive medication, HLA mismatch, depleting induction agents and anti rejection therapy ,neutropenia, co infection with HHV6 and HHV7 and older donor. Use of anti lymphocyte antibody is associated with 2-5 fold increase in the rate of CMV disease.

Clinical Manifestation:

(1) CMV infection : evidence of CMV replication

(2) CMV disease : evidence of CMV infection with attributable symptoms.

CMV disease is further divided into viral syndrome and tissue invasive disease

Late onset of CMV- detection of CMV DNAemia > 100 days after transplantation **.**

Effects of CMV infection:

Direct effects of CMV	**Indirect effects[9] of CMV**
Fever and neutropenia syndrome	risk of opportunistic infection
Pneumonia	risk of graft rejection
Myelosuppression	increase the risk Of PTLD
Gastrointestinal – colitis , ulcers , perforation	increase the risk of HHV6 ,7 infection[8]
Hepatititis	arteriosclerosis / vasculopathy
Pancreatitis	accelerate the atherosclerosis
Chorioretinitis	increase the risk for NODAT

Diagnosis:

- Serology- not useful
- CMV pp65 ag- utilizes the polymorphonuclear cells in peripheral blood. It should be processed within 6-8hours. Easy to perform but immunostaining skills required.
- PCR-detects CMV DNA in whole blood , WBC, plasma and serum.PCR is highly suitable for BAL , CSF and biopsy specimen.
- Hybrid capture assay: rapid detection of viral DNA , less sensitive than PCR
- Branched DNA: less sensitive , reproducible
- NASBA: detects viral RNA and highly sensitive

- Tissue invasive disease has to be proved using culture of tissue involved , histopathology testing with immunostaining, immunohistochemistry or in situ hybridization

Prevention:

Two main strategies - (1) Universal prophylaxis
(2) Pre-emptive therapy

In universal prophylaxis, valganciclovir 900mg/day (now 400mg/day is enough) are all or subset of recipients at risk for 3 months. Valganciclovir is advantageous due to lower pill burden and increased compliance[10].

In preemptive therapy(highly suitable for low risk (D-/R-) surveillance for viral replication is done with pp65 assay or CMV DNA PCR periodically. When threshold genome copies are exceeded, antiviral therapy is started with IV ganciclovir 5mg/kg or oral valganciclovir 900mg and weekly monitoring of copies continued until CMV is no longer detected.

Treatment:

Established clinical proven CMV disease should be treated with intravenous ganciclovir 5mg/kg twice daily, for 3 weeks (to be adjusted for renal dysfunction)

(>70ml/min-5mg/kg evey 12 hr ,50-69ml/min-2.5mg/kg every 12 hrly, 25-49 2.5mg/kg every 24hrly,10-24ml/min 1.25mg/kg every 24hrly, <10ml/min- 1.25mg/kg x3/wk after HD)

Victor trial proved that valganciclovir is non inferior to IV gancicylovir in solid organ transplant recipients with non life threatening disease[11]. Reduction of

immunosuppression should be done in high viral loads , severe life threatening disease, leucopenia .

Weekly monitoring of viral load is essential. Therapy can be stopped only after viral clearance achieved as assessed by PCR or pp65 antigenemia assay. After initial treatment, secondary prophylaxis with valgancicylovir 900mg/day (to be adjusted for renal dysfunction).

(crcl >60ml/min—900mg/day ,40-59ml/min - 450mg/day, 25-39ml/min-450mg every other day, 10-24ml/min -450mgx2/wk , <10ml/min-NR).

In one study 6.2% of CMV isolates had UL97or UL54 mutations determining ganciclovir resistance. In UL 97 mutation only, if low level mutation high dose Iv ganciclovir to be given If no response switch to foscarnet. If UL 54 mutation (normally associated with UL 97 mutation) If GCV-CDV mutation consider foscarnet and adding CMV immunoglobulin. If Ul54polFOS-GCV mutation cidofovir or and half dose foscarnet and GCV[12] to be considered.

BK VIRUS INFECTION:

BK virus has been classified in the polyoma viridae family. Viruses in the group include JC virus , simian virus and monkey polyoma virus besides BKV.

The polyoma virus are a family of small, nonenveloped DNA viruses with icosahedral, capsids 40-44nm in diameter. The genome comprise of

(a) Non coding control region

(b) Early coding region coding for small and large T antigen

(c) Late coding region for viral capsid proteins and agnoprotein[13]

The virus attaches to the host cell plasma membrane through binding of viral capsid protein VP-1. The entry into the cells is through a caveola mediated endocytosis. After entry, virus migrates through cytoplasm, microtubules and nuclear pores into the host nucleus. Ultimately cells are lysed and mature virions are released.[14]

Mode of transmission:

Predominant mode of transmission is the donor allograft as the virus stays latent in the kidney[15]. BKV DNA has been amplified in 0-40% urine samples and 1% nasopharyngeal aspirates of infants with respiratory infection. Feco-oral transmission is also possible .

Clinical features:

Primary infection is common in 80%. Usual manifestation is respiratory illness and occasionally cystitis has been reported. Then virus enters a latent infection and reactivation happens with the development of immunosuppressive states. The reactivation leads to BK virus nephropathy and manifests with renal dysfunction. Progressive renal failure occurs in 30-60% of cases[16]. Occasionally subjects can also present with ureteric obstruction, hydronephrosis and cystitis have been reported.

Risk factors for BKVN:

Donor related : deceased donor, active BKV or CMV infection, donor seropositivity

Recipient related : old age , male , Caucasian race, DM, CMV infection, ATN, absence HLAC7

Transplant related : cold ischemia time, DGF, MMF, tacrolimus, Anti rejection therapy, drug toxicity , ureteral stent placement

Viral related : variant in VP 1, sequence alteration in NCCR

Laboratory Diagnosis:

Diagnosis of BKV infection is based on documentation of viral cytopathic effects (urine decoy cells), the virus itself in blood and urine (Haufman body) and renal histological finding of BK virus nephropathy and serum IgG /IgMantibodies

- Demonstration of BKV inclusion in tubular epithelial or Bowmans capsular epithelial cell
- Plasma BKV DNA>7000copies/ml
- Urine decoy cells>10/cytospin
- Urine BKV >$1x10^7$ copies/ml [17]
- Urine BKVmRNA Rt-PCR >$6.54X10^5$copies/ml[18] are useful to diagnose BKVN

Pathology:

BKV initially affects focally, and is missed in 25% to 37% of samples. Intranuclear viral inclusion bodies in epithelial cells , tubular cell injury and lysis define BKVN. Infected tubules show many cytopathic changes including anisonucleosis of nuclei with hyperchromatasia and smudging and clumping and peripheral margination of chromatin. The nuclei are enlarged and most characteristic is the presence of basophilic intranuclear

inclusion with no halo[19]. Immunostaining of tissue the presence of SV 40 large T antigen is useful for diagnosing BKVN.

Different pathogenesis:

In Acute BKV reactivation → low grade inflammation → leads onto cytotoxic lymphocyte control BKV replication → so reduction of immunosuppression required[20]

In chronic BKV replication → massive inflammation → cytotoxic lymphocytes migrate into Inflammatory area and attack/damage graft cells → reduction of immunosuppression is harmful. Immunomodulation is necessary.

Treatment:

- Reduction of immunosuppression
- Modification of immunosuppression :Tac→CyA or Tac → siro, MMF → leflunomide
- Discontinuation: of Tac or CyA or MMF –continue with double therapy

Two drugs has shown to be effective—cidofovir and leflunomide

Fluroquinolone antibiotics have also shown to improve graft function[22]

HEPATITIS C VIRUS:

Hepatitis C virus is a flaviviridae family. Six HCV genotypes with several distinct subtypes has been identified. As virus replicates over time, selective pressures from the

immune system or antiviral treatment or both cause viral population to evolve. This mutant version of genotype is called as quasispecies.

Impact of pretransplant Hepatitis C on post transplant outcome:

Orloff and collegues[23] reported the liver biopsy findings at 3 to 7 year after kidney transplantation in HCV positive subjects are 12% have chronic active hepatitis, 50% have mild hepatitis and 38% had normal histology. HCV has no adverse effect on graft survival. Lee and coworkers[24] told that HCV infection did not reduce renal allograft or patient survival. But if more liver disease, greater prevalence of sepsis in the HCV infected recipients.

Periera and coworkers[25] computed that the recipients who are HCV positive before transplantation, relative risk of post transplantation liver disease was 5, graft loss was 1.3 and death was 3.3

NODAT and Hepatitis C:

NODAT develops within 36 months of kidney transplantation in upto 24% of patients[26]. HCV infection is associated with increased insulin resistance. There was eight times increase in NODAT in patients treated with tacrolimus (58%) compared with cyclosporine (7.7%)[27]

HCV associated Post transplantation glomerulopathy:

Chronic HCV infection has been associated with the development of mixed essential cryoglobulinemia[28]. Nearly half of HCV infected patients who have type 2 or 3

cryoglobulinemia develop renal complication, including MPGN and membranous nephropathy.

Disease progression:

HCV viral loads increase approximately 1.0 to 1.5 log $_{10}$IU/ml after transplantation.

Treatment :

Treatment of HCV in transplant recipients are not recommended because of risk of precipitating acute rejection. There are clinical circumstances in which risk – benefit assessment to be done. HCV associated glomerulonephritides can recur after kidney transplantation and cause progressive renal dysfunction and antiviral therapy is needed to prevent the graft loss. Severe cholestatic hepatitis and cryoglobulinemic vasculitis need IFN therapy.

Acute rejection has been reported in several published studies with rates varying from 15 to 64% who were treated with interferon. IFN with ribavirin combination therapy is better if the patient has no graft dysfunction. In renal transplant recipients, ribavirin tolerance varies. Associated hemolytic anemia require high amount of rhEPO or ribavirin dosage modification.

HEPATITIS B INFECTION:

A recent systematic review and metaanalysis estimated that 3.07% of non tribal and 11.85%of tribal population . HBV is hepatotropic virus enveloped , partially double stranded DNA virus that is a member of hepadna virus family. The genome of HBV encoded 4 different genes. The C gene encodes the hepatitis core antibody and the P gene encodes the

hepatitis B polymerase, the S gene encodes 3 different polypeptides of surface antigen or protein and the X gene encodes proteins potentially involved in transactivation of viral replication.

HBV after renal transplantation:

Fabrizi and collegeues[30] shows that Hbs Ag seropositivity was an independent risk factor for death after renal transplantation with a relative risk of 2.49. Immunosuppression may stimulate HBV replication by a variety of mechanism for instance by diminishing activity of cytotoxic T lymphocytes. In addition a glucocorticoid responsive element that enhances the replication[31] and Azathioprine and CNI also enhance replication . Krishnamoorthy et al[32] 4.5% post transplant seroconversion among those previously negative and 20% among those who are anti HBc positive.

Two different stratagies to prevent HBV are prophylactic and preemptive treatment stratagies. Prophylaxis is given only to those who have detect a DNA or HBs ag or all HBV infected patients. In the preemptive strategy, a new appearance of HBV DNA or 10 fold rise in HBV DNA level result in requiring treatment. Lamivudine dramatically improved the 10 year survival rate from 55% to 90%. IFN is not used ,it can cause steroid resistant rejection , tubulointerstitial nephritis and direct nephrotoxicity. Since lamivudine is prone to develop resistance, entecavir is used .Telbivudine and tenofovir have not been studied in renal transplantation. Combination therapy with multiple anti viral agents may be necessary if resistance develops.

HERPES GROUP OF VIRUSES:

VARICELLA ZOSTER VIRUS:

Human herpes virus belongs to alpha herpes virinae. It produces 2 types of disease

1. 90% of patients –herpes zoster
2. 10% of patients –at risk of primary infection

Incidence 4-12%[33]

Produces a localized dermatomal zoster or multidermatomal or disseminated Zoster with or without visceral involvement. Median time of onset- 9 month[34].

Complication

DIC and hepatitis and pneumonitis and in primary infection pancreatitis and orchitis and rarely infection of allograft and encephalitis are documented.

Diagnosis :

Culture of varicella zoster in cell lines , Tzanck smear.

Pre transplant screening for previous VZV infection should be performed and naïve patients should be vaccinated. But it is a live vaccine, transplant should not be proceeded within 4 to 6 weeks. A VZV naïve transplant patient who is exposed to someone infected with varicella should receive varicella immune globulin within 96 hours of exposure.

HERPES SIMPLEX VIRUS INFECTION:

Human herpes virus 1- HSV – sub family alpha herpes virinae. Prevalence-53% Herpes simplex most commonly cause reactivation infection . Following primary infection the virus stayed in the sensory ganglia. In the absence of prophylaxis , HSV seen in the first month after transplantation.

Reactivation or Primary HSV infection results in oral or mucocutaneous lesion , hepatitis[35] and pneumonitis, tracheobronchitis, esophagitis. Disease may be severe and prolonged in viral infection.

HSV is the most common cause of encephalitis in transplant recipients. Esophageal ulcer produced by HSV can mimick candida. Mutivisceral infection is fatal.

Diagnosis:

Direct fluorescence antibody from vesicular lesion, HSV PCR in CSF or visceral tissue sample.

Treatment:

Effectively treated with acyclovir. Acyclovir resistance may arise from mutation in the genes for thymidine kinase or DNA polymerase. Foscarnet, cidofovir, topical trifluridine considered for resistant strains[36].

HUMAN HERPES VIRUS 6, 7 :

It belong to subfamily of betaherpes virinae, genus Roseola virus. Both viruses are highly prevalent in adults. After the primary infection, these viruses enter into a latency and

that remains in the host for life long time. Both viruses are lymphotropic. Most infection in renal transplant recipients are due to HHV 6.

- HHV6 useCD46 molecule as a receptor- infects lymphocytes , monocytes, epithelial, endothelial cells.
- HHV7-use CD 4molecule as a receptor- infects only lymphocytes.

HHV 6 - produce fever, rash, encephalitis, hepatitis, myelosuppression, interstitial pneumonitis

Both viruses

(a) have immunomodulating properties.[37]- have the ability to change the expression of immune activation molecule, modulate the expression of cytokines and induce apoptosis.

(b) HHV 7 act as a cofactor for HHV6 and CMV reactivation

(c) HHV6 and HHV7 act as a cofactor for CMV disease and acute rejection.

Diagnosis:

Quantitative and qualitative molecular assay, tissue immunohistochemistry, peripheral blood mononuclear cell culture.

Treatment:

Reduction of immunosuppression and ganciclovir, foscarnet and cidofovir tried.

HHV 8:

Belongs to subfamily of gamma herpes virinae.

It is associated with Kaposi sarcoma, primary effusive lymphoma, muticentric castleman's disease. Transplant associated Kaposi sarcoma 0.2 to 5% of renal transplant recipients. Of all the tumous, Kaposi sarcoma occurs at the shortest interval. It is due to upregulation of VEGF in vascular endothelial cells.[38]

Treatment:

Reduction of immunosuppression, chemotherapy , change into sirolimus.

EBSTEINBARR VIRUS:

Belong to Gamma herpesvirinae, genus-lymphcryptvirus.

In transplant recipients, primary EBV infection produces a mononucleosis type syndrome with or without lymphadenopathy or pharyngitis. Meningitis , hepatitis and pancreatitis are noted. EBV infection remits and relapses in children.This syndrome suggest relative overimmunosuppression

EBV plays a role in the development of PTLD[39]. EBV increase the risk 10 to 76fold. Post transplant Nonhodgkins lymphoma is common complication. PTLD in transplant recipients has increased extranodal involvement, poor response to conventional therapy and poor outcome. Most of the disease, the origin is B cell . PTLD occuring late >1to 2 years after transplantation are EBV negative.

Clinical presentation:

- Fever, mononucleosis like syndrome,
- Gastrointestinal bleeding , obstruction or perforation
- Abdominal mass lesions infiltrative disease of allograft
- Hepatocellular or pancreatic dysfunction
- CNS disease

Diagnosis:

- Quantitative EBV viral load testing- serial assay are useful[40]
- Use whole blood sample rather than plasma sample

Management:

- Reduction of immunosuppression
- Combination of anti B cell therapy(rituximab)
- CHOP regimen[41]
- Adoptive immunotherapy with stimulated T cells

<u>PARVOVIRUS B19</u>:

It is a small , non enveloped single stranded DNA virus-parvoviridae family-erythrovirus genus.

B19 genome encodes 2 structural capsid proteins VP1, VP2.

Pathogenesis:

B19 virus targets the erythroid progenitors in the bone marrow by binding to glycosphingolipid globoside also known as blood group antigen P antigen[42] is expressed in more in erythroblasts The existence of cellular coreceptor integrin is necessary for successful infection. Integin is expressed in erythroid progenitors . Ku80 also act as a possible coreceptor[43].

After B19 infection of erythroid progenitors , cell death ensues either by cell lysis or by apoptosis mediated by NS1 protein.

Clinical manifestation:

Anemia is the predominant clinical manifestation. In normal hosts, at approximately 8 days after infection parvovirus induces the lysis of RBCS and prolonged for about 10 days. But in immunocompromised state it produces a chronic anemia. Onset of anemia has been reported from 2 week to 63 month after transplantation.

Renal manifestation- proliferative glomerulonephritis, collapsing glomerulopathy[44], thrombotic microangiopathy and acute allograft rejection and renal transplant dysfunction

Liver dysfunction, fibrosing cholestatic hepatitis , encephalitis and cerebral vasculitis.

Diagnosis:

Parvo virus DNA by PCR

Bone marrow- pure red cell aplasia- reduction of erythroid cell lineage and giant erythroblasts.

Treatment:

- Commercial IV Ig useful
- Reduction of immunosuppression
- spontaneous remission in some patients.
- Switch from Tacro to cyclosporine[45].

ADENOVIRUS:

It is a nonenveloped , double stranded DNA viruses

Has 51 immunological distinct types which are further classified into 1to6(A-F) subgroups on the basis of hemagglutinin properties , DNA homology , oncogenic potential and clinical disease. Incubation period is from2 days to 2 weeks. It is a rare pathogen in kidney transplant recipients. The most common manifestation is hemorrhagic cystitis[46]. Other manifestion is pneumonitis and pyelonephritis , necrotizing tubulointerstitial nephritis and gastroenteritis and necrotizing hepatitis

Diagnosis:

Adenovirus DNA PCR in the blood and urine

Treatment:

- Reduction of immunosuppresion
- IVIg
- Cidofovir and ribavirin

HUMAN PAPILLOMA VIRUS INFECTION:

HPV are small DNA viruses and it infects epithelial tissues of skin and mucous membranes. Among 100 distinct subtypes, 15 subtypes have been designated with invasive cervical cancer.

Clinical manifestation:

It is the important cause of more than 90% of cervical and anal cancers and a large proportion of vaginal and penile cancers and also head and neck cancer. HPV – 16 accounts for 50% cervical cancer. Most common clinical manifestation is anogenital and cutaneous warts and condyloma. HPV 6 and 11 produce genital warts and also respiratory papillomatosis. HPV 1 produce palmar and plantar warts.

Diagnosis:

- Elisa for IgM and IgG for HPV
- HPV DNA PCR
- Histology

Treatment :

- ❖ Topical salicylic acid/lactic acid or imiquimod cream 5% 3 times per weekfor 16 weeks[47]
- ❖ Cryotherapy q1-2 weeks of liquid nitrogen spray
- ❖ If not responded-surgical removal.

HIV INFECTION:

HIV virus belong to retroviridae, genus lentivirus

HIV is not a contraindication for renal transplantation

Pts CD4 count >200cells/cumm for atleast 6 months and undetectable HIV viremia <50copies/ml and demonstrable adherence and a stable HARRT regimen for >6 months and absence of AIDS defining illness is the inclusion criteria for renal transplantation.[48]

Main challenges in the clinical management of renal transplant recipient are pharmacological interaction between immunosuppressive drugs and HAART therapy and higher rate of acute rejection (upto 25%)

RESPIRATORY VIRUSES:

Various viruses can cause respirapry disease in renal transplant recipient including adeno, parainleunza, influenza, RSV, rhino, corona virus. These viruses can lead to upper respiratory tract disease as well as bronchitis , pneumonitis and pneumonia

Treatment:

- Supportive care influenza
- Treated with ostelmivir or zanamavir
- Amantadine is not recommended because it treats only influenza and produces the resistance
- Ribavirin for Respiratory syncytial virus

MATERIALS AND METHODS

Study Place	:	Department of Nephrology
Study Design	:	Cross-sectional descriptive prospective and retrospective study
Period of study	:	Two years
Study population	:	Patients attending the Transplant clinic, Nephrology Department in Rajiv Gandhi Government General Hospital.
Ethical approval	:	Obtained from ethical committee headed by Dean, Madras Medical College.
Consent	:	Obtained from all patients

Inclusion criteria:

Renal transplant recipients diagnosed with viral infections diagnosed by either clinical or laboratory evidence or serological methods or radiological or by renal biopsy

Exclusion criteria:

Renal transplant recipients with empirical antiviral therapy given.

This study was done in prospective and retrospective manner. Retrospective cases selected by examining the case records and examining the patients while coming for follow up and in prospective cases are followed during the time period of study.

All the selected transplant recipients underwent detailed history and clinical examination. Some of the viral infections diagnosed by clinical examination alone like varicella Zoster and cutaneous warts caused by human papilloma virus.

All the patients undergo routine blood investigations like complete hemogram and urine routine and urine culture and peripheral smear and renal function tests and liver function tests and blood sugar and serological tests wherever necessary. All the patients were undergone USG KUB and Doppler wherever necessary was done.

CNI level was done whenever necessary we prefer to take Co level by chemiluminescence method providing that patient not having diarrhea at that time and confirming regular compliancy

Renal biopsy was done in selected patients whenever necessary like graft dysfunction or proteinuria. Before renal biopsy HBS Ag, anti HCV and HIV antibody by ELISA and coagulation parameters and bleeding time and platelets to be done. In our department, renal biopsy is performed under ultrasound guidance with needle biopsy gun. Patient lies in supine position. Upper pole of the kidney is marked . Lower pole of kidney is avoided in contrast to native kidney biopsy. After infiltration with 2% lignocaine, stab incision is made using a 11G blade. While asking the patient to hold breath, 16G biopsy needle gun is fired to get the sample. Patient is then asked to lie flat for 12 hours, with strict monitoring of pulse, blood pressure and urine output. Biopsy sample was sent in formalin & Michel's fixative for light microscopy (LM) and Immunoflourescence (IF) respectively. All the biopsy samples were reported by single nephropathologist to avoid bias.

For LM, all samples were stained with hematoxylin and eosin (H&E), periodic acid - Schiff (PAS), Masson trichrome and Jones silver methenamine. For IF,3 µ sections were stained with florescent tagged antibodies to IgG, IgM, IgA, C_3, $C1_q$, fibrinogen, Kappa and lambda chains, c_4d. For suspecting BK virus immunohistochemistry using SV 40 staining was done and suspected EBV immunhistochemistry was done.

Radiological investigation X ray chest and USG abdomen and CT chest was done whenever necessary and PET scan was done whenever necessary.

If presented with pulmonary involvement bronchoalveolar lavage was done and BAL fluid sent for cytology and culture analysis.

If presented with CNS involvement , CSF fluid sent for quantitative PCR.

If presented with Gastrointestinal tract involvement, mucosal biopsy and upper GI endoscopy and colonoscopy was done.

If presented with cutaneous involvement or mucocutaneous involvement , scraping and examine Tzanck smear preparation was done.

Those patients with fever, leucopenia and graft dysfunction suspected to cytomegalovirus infection, CMV pp65 antigen is tested . Blood was sent through EDTA anticoagulated tube and analysed within 6-8 hrs It is measured in the form of $>10/2X10^5$ neutophils. If the total WBC count was less than 1500 either we will repeat pp65 antigen or CMV DNA PCR because it may be false negative. After finishing of treatment , we are again monitoring for viral clearance. Sometimes renal allograft biopsy shows viral inclusion body.

For suspecting BK virus either doing immunohistochemical staining with SV40 or by quantitative DNA PCR in the blood. We are not doing urine BK DNA PCR due to logistic reasons. Renal biopsy shows viral inclusion body in the tubular epithelial cells.

In patients with acute hepatic dysfunction hepatitis A and E virus antibody and chronic dysfunction Hepatitis B and C virus was done. If it was positive quantitative PCR was done and portal Doppler and Usg abdomen was done. Liver biopsy was done before starting treatment in Hepatitis c and hepatitis B. We are not doing liver biopsy in regular basis before starting of treatment. We are regularly monitoring of viral load by every 3rd monthly or 6^{th} monthly. If patient develops cirrhosis of liver then doing ascitic fluid analysis was done.

If the patient develops anemia suspecting to be parvovirus quantitative DNA PCR was done and bone marrow aspiration was done to confirm the erythroid cell lineage affection and reticulocyte count was monitored.

In suspecting Herpes simplex virus infection, in encephalitis CSF quantitative PCR was done and in cutaneous involvement, Tzanck smear examination was done.

For suspecting EBV , PET scan was done to find the increased FDG uptake and immunohistochemical staining of renal biopsy or lymphnode biopsy and antibody to EBV screening and quantitative PCR was done.

For those patients having gross hematuria, suspected to be adenovirus, quantitative PCR adenovirus to be done.

If the patient present with rash with leucopenia CMV serology was negative, then suspect HHV6 or HHV7 infection and then quantitative PCR to be done.

If the patient found to be HIV serology was positive, then CD_4count and then followed up regularly and monitor for drug interaction.

Statistical analysis:

Baseline characteristics of all patients were presented descriptively with mean ± SD for continuous variables and percentage for categorical variables. We used Mann-Whitney test for univariate comparison of continuous variables and Fisher exact t test for categorical variables. Multivariate analysis was done by binary logistic regression analysis. p value of less than 0.05 was considered as statistically significant. It was performed using medcalc software.

RESULTS AND OBSERVATION

There were 356 patients were analysed in a prospective and retrospective manner.

Mean age of recipient - 29.8 years

Mean age of donor - 41.7 years.

Male: female - 3.7:1

Live: cadaver - 4.08:1

Immunosuppressive regimens:

CSA/AZA/PDN - 33 (65.4%)

CYCLO/MMF/PDN - 46 (12.9%)

TACRO/MMF/PDN - 75 (21.0%)

TACRO/AZA/PDN - 2(0.5%)

Induction therapy was given—8 patients.

ATG - 3 patients

IL2 receptor antagonists- 5 patient

Total infective episodes - 741.

VIRAL INFECTION:

Total no. of viral infective episodes - 224

Total no. of persons affected by viral infection - 152.

42.6% of patients affected by viral infection.

On an average 72 persons have more than one viral infective episode.

Male: female - 3.47:1

Live : cadaver: 5.04:1

Onset of viral infections:

Phase I (<1 month) - 9 episodes(4%)

Phase II (1-6 month) - 74 episodes (33%)

Phase III (>6 month) - 119 episodes (53.1%).

Pre transplant hepatitis C positive - 20

Pretransplant hepatitis B positive - 2

Risk factors:

NODAT : 53persons (34.8%)

ART : 55 persons (36.1%)

CNI toxicity : 44 persons (28.9%)

Risk Factors	With viral infection	Without viral infection	p value
NODAT	53	27	<0.001
Anti rejection therapy	55	45	<0.004
CNI toxicity	44	76	0.113

NODAT and ART is the significant risk factor for the development of viral infection.

Outcome :

GDF -51 (33.5%)

Graft loss - 15 (9%)

Death -18 (11.8%)

Outcome	GDF	Graft loss	death
With viral infection	51	15	18
Without viral infection	71	55	78
p value	<0.001	<0.001	<0.001

Viral infection is one of the most contributing factor for the persistent graft dysfunction and graft loss and death of the patient.

Cytomegalovirus infection:

Total persons affected by CMV-62

Male : female : 46:16

Live : cadaver - 54:8

Prevalence of CMV infection—17.4%

Mean time of onset –4±1month after transplantation.

- Phase1 (<1 month)-1
- Phase II (1-6 month)-40(64.5%)
- Phase III (>6 month)-21(33.8%)

Clinical manifestation:

- CMV syndrome - 37
- Skin/palatal /oral ulcer- 9
- Pneumonitis - 7
- Encephalitis - 1
- Retinitis - 2
- Colitis - 12

Retinitis present in late CMV infection.

Leucopenia is present in 72.5% of patients. It is the one of the associative factor in active CMV infection. (p value -<0.001)

Risk factors:

Risk factors	With CMV	Without CMV	p value
NODAT	15	65	0.7387
Anti rejection therapy	27	83	<0.03
CNI toxicity	24	100	0.556

Anti rejection therapy is the most contributing factor for development of CMV infection.

Associated other infections:

Other Infections	Fungal infection	TB	Bacterial infn	Other viral infn
CMV +ve	19	6	18	22
CMV-ve	26	29	162	130
p value	<0.01	1.07	<0.002	<0.002

CMV infection is a risk factor for developing bacterial and other viral infection and fungal infection (p Value <0.05) but not for tuberculosis.(P-1.07 – not statistically significant)

Recurrent CMV – documented in 3 patients.

1 patient developed resistance to gancicyclovir

Outcome:

Outcome	**GDF**	**Death**
CMV+ve	28	14
CMV-ve	94	82
p value	<0.05	0.434

Among the viral infections, CMV and BK virus are the commoner viral infections producing persistent and progressive graft dysfunction. In CMV infection GDF persistence (45.1%) is statistically significant.

	GDF	**Death**
Early onset of CMV	13	5
Late onset of CMV	16	12
p value	<0.032	<0.005

Compared to early onset CMV, late onset CMV is the more significant contributing factor for patient survival.

BK VIRUS INFECTION:

Total no. of patients - 3

Male:female - 2:1

Live:cadaver - 2:1

Prevalence - 0.8%

Mean time of onset of transplantation-8 month ± 4 month after transplantation.

Comorbidities:

H/O anti rejection therapy- 1

Associated herpes Zoster - 1

Presentation:

Ureteric stenosis - 1

Interstitial nephritis - 1

Outcome	GDF
BK virus infection	3
p value	<0.039

All 3 patients affected by BK virus have persistent graft dysfunction.

Since logistic reasons BK virus qualitative DNA not done in everybody & only urine decoy cells were sent. If it is positive , we will do DNA PCR. That is the reason it is less prevalence in our study.

HEPATITIS C VIRUS :

Total no of patients affected by HCV+VE - 63

Male : female - 45:18

Live: cadaver - 52:11

Pre transplant Hepatitis C positive - 20.

Mean onset of HCV infection - 14±2.6 months after transplantation.

Prevalence including prêtransplant positivity - 17.6%

excluding pretransplant positivity - 12.07%

.H/o blood transfusion at the day of transplant - 8

Associated with other infection:

Hepatitis B - 7

Fungal infection - 16

TB - 6

CMV - 8

Herpes zoster - 3

Risk factors :

Risk factors	HCV^{+ve}	HCV^{-ve}	p value
Antirejection therapy	15	85	0.443
CNI toxicity	14	110	0.125

Both ART and CNI toxicity are not coming as a statistically significant risk factors.

Presentation:

liver enzyme elevation - 20

Incidental - 28

Clinical jaundice - 15

Liver biopsy was done in 4 patients. One patient had fibrosing cholestatic hepatitis but not treated with interferon. Patient died before treatment. Other 3 had chronic active hepatitis.

Outcome:

Outcome	NODAT	GDF	Death
Hep C +ve	35	19	5
Hep C -ve	45	113	91
p value	<0.009	0.2506	<0.001

55.5% of patients developing NODAT in HCV+ ve patients. (p value <0.009)

USG shows cirrhosis of liver - 4 patients

HEPATITIS B INFECTION:

Total no. of patients - 16

Male: female - 14:2

Live:cadaver - 14:2

Prevalence without previous infection- 3.9%

With previous infection - 4.4%

Pre transplant hepatitis B –2 Patients.

Mean duration of detection of hepatitis B - 13±2 months

- Phase 1 (<1 month) - nil
- Phase 2 (1-6 months)-1
- Phase 3 (>6 month)-13

Risk factors:

Risk factors	With Hep B	Without Hep B	p value
Anti rejection therapy	5	105	>1.0
CNI toxicity	3	121	0.1919
GDF	5	117	>1.0

Most of risk factors described in viral infection are anti rejection therapy and CNI toxicity and GDF. But no factors are came as statistically significant in my study for hepatitis B infection.

H/o blood transfusion - 4 patients out of 14 patients after transplant.

Associated other infection:

Hepatitis C - 7

Herpes zoster - 2

Herpes labialis - 3

Outcome:

Outcome	NODAT	Death
Hep B +ve	6	3
Hep B –ve	74	93
p value	0.214	0.572

NODAT is present in 37.5% of patients. Since all 6 are associated with hepatitis C, it is not applicable only to hepatitis B.

Presentation

- Liver enzyme elevation - 5
- Incidental - 7
- Clinical jaundice - 5

Only one case of TMA is documented and one case of cresentic glomerulonephritis is documented.

Liver biopsy was done in 2 patients. 2 patients had chronic active hepatitis.

Treatment was started on 5 patients. 4 patients started on lamivudine naïvely and 1 patient started on entecavir naïvely. Out of lamivudine started patients, out of 4, three patients developed resistance to lamivudine and started on entecavir.

In 2 patients USG shows cirrhosis of liver. Both 2 are Hep C and Hep B positive.

HERPES ZOSTER INFECTION:

Total no. of patients - 29

Male: female - 24:5

Live:cadaver - 23:6

Mean time of onset- 9 months after transplant.

Prevalence - 8.1%

- Phase 1 (<1month) - 3
- Phase 2 (1-6month) - 11
- Phase3 (>6month) - 15

Complication:

Encephalitis - 1

Recurrence - 2

Severe Post herpetic neuralgia - 2

Associated other infection:

CMV - 2

BK virus - 1

HCV - 2

Hepatitis B - 1

Risk factors:

Risk factors	With herpes zoster	Without herpes zoster	p value
Anti rejection therapy	13	97	0.0971
CMV	2	60	<0.01
CNI toxicity	8	116	0.425
NODAT	9	71	0.356

Eventhough antirejection therapy and NODAT and CNI toxicity described as risk factor, it is not statistically significant but associated CMV infection is considered as a strong risk factor for developing herpes zoster infection.

Out of 29 patients , 16 patients have multidermatomal involvement.

Risk factors	Multidermatomal	Single Dermatomal	p value
Anti rejection therapy	11	2	<0.007
NODAT	5	4	1.0
CNI toxicity	6	2	0.237
CMV	2	0	0.487

For mutidermatomal herpes zoster involvement antirejection therapy is the strong risk factor (p value<0.007)

Outcome:

Outcome	GDF	Death
With herpes zoster	8	3
Without herpes zoster	114	93
p value	0.541	<0.04

Graft dysfunction is higher in patients developing herpes zoster , it is not statistically significant. But death occurs in 3 patients. Eventhough it is statistically significant, that patients had also CMV infection and fungal infections.

CHICKEN POX INFECTION:

- Total no. of patients - 11
- Male : female - 9:2
- Live : cadaver - 7:4
- Mean time of onset - 6month $\pm$ 2month

Occurrence :

- Phase 1 - <1month - 2
- Phase 2 - (1-6month) - 4
- Phase 3 - (>6month) - 5

Types of presentation:

- Diffuse disease - 4
- Localised disease - 6
- Hemorrhagic disease - 1

Complication :

- Encephalitis - 1
- pneumonia - 1
- pancreatitis - 1

Comorbidities:

- HCV - 2
- CMV - 1
- Herpes zoster - 1

Risk factors:

Risk factors	Chicken pox	No chickenpox	p value
NODAT	4	76	0.275
Anti rejection therapy	3	117	0.756

36% of patients have NODAT and 27% of patients had anti rejection therapy but it is not statistically significant.

Outcome:

Outcome	GDF	Death
Chicken pox +ve	2	2
Chicken pox-ve	120	94
p value	0.106	0.733

Death occurred in 18.18% of patients. Persistent graft dysfunction occurred in 18.18% of patients.

HERPES SIMPLEX INFECTION:

- Total no. of patients - 23
- Male : female - 21:2
- Live : cadaver - 20:3
- Mean Time of onset - 7month $\pm$ 3 months after transplantation
- Prevalence - 6%

Presentation :

- Oral/palatalulcer - 5
- Herpes simplex labialis - 14
- HSV pneumonia - 1
- Esophageal ulcer - 1
- Scrotal ulcer - 1
- Preputial ulcer - 1
- Encephalitis - 1

Associated with other infections:

- CMV - 3
- HCV - 2
- Herpes zoster - 4

Risk factors:

Risk factors	Herpes simplex	Without herpessimplex	p value
NODAT	5	75	1.0
Anti rejection therapy	6	94	1.0
CNI toxicity	12	112	0.118

NODAT is present in 5 patients only.

Outcome:

Outcome	GDF	Death
Herpes simplex +ve	6	2
Herpes simplex –ve	116	94
p value	0.498	<0.050

2 Patients died. One patient has encephalitis and one patient had pneumonia.

HHV6 VIRUS INFECTION:

- Only one patient is considered as HHV6 infection
- Presentation - exanthematous fever
- Risk factor: CMV+ve

EBSTEIN BARR VIRUS:

- Total no. of patients - 2
- Both patient had graft dysfunction

One patient had a history of ART and treated CMV with renal biopsy shows plenty of interstitial lymphocyte infiltration. One patient is present as pulmonary nodule and hilar lymphadnopathy

PARVO VIRUS:

- Total no.of patient-3
- Male:female=2:1
- Live:cadaver=2:1
- Prevalence-0.8%

Associated with other viral infection:

- HCV-1

Other risk factor:

- Graft dysfunction-1
- CNI toxicity-1
- 2 patients present as pure red cell aplasia
- One patients had collapsing glomerulopathy.

ADENOVIRUS:

- Total no.of patients:3
- Male:female=2:1
- Live:cadaver=2:1
- Prevalence-0.8%
- Mean time of onset –3 month$\pm$1 month after transplantation.

Presentation:

- 2 patients have hematuria
- 1 patient had interstitial hemorrhage in biopsy

Associated with other infection:

- Herpes zoster-1
- HCV-1

Risk factors:

- NODAT-1
- ART-1

Outcome:

- GDF-2
- Graft loss-1

HUMAN PAPILLOMA VIRUS:

- Total No. of patients - 7
- M : F - 6:1
- Prevalence - 1.9%
- Mean time at the onset - 18 month ± 6 month after transplantation.
- Presentation as a cutaneous warts - 7

Risk factors:

- ART-1
- NODAT-1

Associated with infection:

- HCV - 1
- herpes zoster - 1

HIV INFECTION:

- Only one patient had ELISA positive after 1½ year.
- H/o blood transfusion after transplant.
- No h/o other hepatitis b or c infection
- No h/o sexual misconduct or IV drug abuse.
- Presently no opportunistic infection present.
- CD4 count - 300cells/cu.mm

DISCUSSION

In our study 356 patients were taken. Out Of which 152 persons were affected by viral infection. 42.6 % affected by viral infection.

Total Number of viral infective episodes were 224. Total infective episodes 741. Bacterial infection excluding mycobacterium TB accounts for 45%. Viral infections accounts for 30.5%

Fungal infection accounts for 9.5% and mycobacterium TB accounts for 10.8% and parasitic infection accounts for 5.2%. Dharnidharka et al [49]Bacterial infection are twice as frequent as viral infections and among bacterial infections vascular access and urinary tract infections are the commonest and among viral infection cytomegalovirus infection is the commonest.

We divided into 3 phases . I phase- less than one month after transplantation. II Phase 1-6 months. III phase more than 6 months. Out of 3 phases Phase III has more viral infective episodes (53.1%) and followed by Phase II (33%) and lastly Phase I (4%).In Phase II CMV infection is the commonest. Stratta et al[50] opine that 1st month bacterial infection is the commonest and 2nd - 4th month CMV predominates the bacterial and mean timing of bacterial infection is 60 days and mean onset of CMV is 70 days and non CMV viral is 145 days and fungal is 163 days

Most of the risk factors analysed for developing viral infection are state of immunosuppression and antirejection therapy and NODAT and CNI toxicity and graft dysfunction . In our study anti rejection therapy (p-0.004) and NODAT(P-0.001) are the significant risk factors for developing viral infection.

In the outcome analysis, 53.5% of viral infected persons have persistent graft dysfunction. The Graft loss occur in 9% of persons in our viral infected study population and death occurred in 11.8% of patients. Viral infection is one of the major determining factor for graft and patient survival.

CMV infection:

Prevalence of CMV disease in our study is 17.4%. The risk of CMV infection depends on the serology and immunosuppression and antiviral prophylaxis. In our hospital we are not checking for the serology status of recipient and donor and also not giving prophylactic antiviral therapy for all patients. Most of the studies are representing the incidence of CMV infection between 8 to 32%. Kotton Cn etal with conventional immunosuppressive regimens 10 to 15% of get active CMV infection[33]. Kanter et al 32 patients (15.7%) had active CMV infection[51]. In our study mean time of onset of CMV infection is 4±1 month. Green et al in the absence of prophylaxis the mean time of detection of CMV is between 1-3 months[52]. In the presence of prophylaxis seen after 90 days.

In our study around 65% of disease occur in less than 6 month. Late onset of CMV infection occur in 34% of our study population. Helantra et al[53] late onset of CMV infection 47/127(37%) of patients.

Most common presentation of CMV is cytomgalovirus syndrome . In our study 37 patients (59.6%) had CMV viral syndrome. Arthurss et al [54]said about CMV syndrome accounts for 60% of all cases of CMV disease. Colitis present in 19.3% of patients. Halentra etal[53] in his study colitis present in 24/127 (18.3%) of patients. Retinitis is present in late onset of CMV disease[55]. In our study 2 patients present in late after 6 months only (3.2%)

.Arthurs et al [54] in his study 2% of patients with retinitis. Leucopenia present in 72.5% of patients . it is the significant risk factor and also severity of CMV disease in our study.

Recurrent CMV occur in 3 patients in our study (5%). Halenthra et al[53] in his study 19% had recurrent CMV. In our study late onset CMV disease 2 patients develop resistance to ganciclovir. V Jha et al[100] 15% of late onset disease was due to drug resistant strains. In our study 9.2% of late onset disease due to drug resistant strains. This is less comparatively because of not using prophylactic therapy.

Risk factor analysis, eventhough CNI level and toxicity and NODAT correlating with high incidence of infection, our study anti rejection therapy and rejection is the statistically significant risk factor for CMV infection. Boratynska M [56]et al told that acute rejection is a major risk factor for CMV disease and disease occur in three quarters of patients during the month following an episode of rejection . In our study 46% had h/o rejection and Anti rejection therapy.

Invasive bacterial and fungal infection are highly associated with CMV diseases because proinflammatory condition associated with infection reactivate the virus. Conversely CMV disease increase the risk of opportunistic bacterial and fungal and other viral infection[57]. In our study also, CMV is the statistically significant risk factor for bacterial and fungal and other viral infection but not with mycobacterium tuberculosis.

CMV infection is the risk factor for graft dysfunction and graft loss. Our study CMV is significant predictable risk factor for graft dysfunction and death. S Sagedel [57] etal told that CMV disease is the independent risk factor for overall mortality beyond 100 days of post transplantation and reduced graft survival.

Comparing the early and late onset of CMV infection , late onset of CMV infection is more correlating with graft dysfunction and mortality. Limaye AP etal[58] said that late onset disease is a strong predictor of mortality and graftloss. Our death rate was 22.5%. In Arthurs Sk et al[54] study 20% of patients died

BK virus :

In our study prevalence-0.8%. Most of the studies[59] quoting 1%-10% of renal transplant recipients acquired BK virus infection In our study it is less because due to logistic reasons we are not done DNA PCR and only doing urine decoy cells if it is positive then only we are doing, so it may lesser than the actual value. Mean time of onset in our study – 8 month . Most of the studies[60,61] show occurs within one year and also 1-3 months and beyond 1 year also.

All the 3 patients now with graft dysfunction. Ramos et al[15] in n BK virus infection, progressive renal failure occurs in 60% of patients. One patient presenting as a ureteric stenosis. Gupta etal[62] described BK virus can cause ureteric stricture and hydronephrosis.

Two patients had intersitital nephritis. Howell Dn etal[63] describes the interstitial infiltrates and tubular cytopathic changes in BKVN. In Biopsy one patient had intranuclear viral inclusion bodies in epithelial cells. Nickeleit etal[64] told that intranuclear viral inclusion bodies in epithelial cells along the entire nephron and the transitional cell layer are hall marks of BK virus nephropathy. Affected tubular cells are enlarged and often necrotic.

Hepatitis C infection :

Prevalence of Hepatitis C in post renal transplant recipients in our study 17.06% including pre transplant Hepatitis C positive if we excluded the pre transplant positive recipients then it is 12.5%. Most of the studies [65-67] said the prevalence varies from 6% -46%. In our study cirrhosis occurs in 6.3% of patients. Many studies report[68,69] that cirrhosis is 5 to 21% during 3 to 7 year follow up.

NODAT is seen in our study 55.5%. Cosio FG et al[70] his study 24% of patients develop NODAT. HCV is the strong statistically significant risk factor for NODAT in our study. A recent meta analysis[71] of 10 studies in 2502 renal transplant recipients showed a strong link between anti HCV seropositivity and post transplantation diabetes .

Acute rejection episode in our study was 23.8%. Jose Maria Morales[72] et al in his study acute rejection rate was 32.5% and biopsy proven CAN was 34.4%. In our study biopsy proven IFTA 20.6%.

Only one patient had fibrosing cholestatic hepatitis and patient was died before starting of IFN therapy. IFN treatment of renal transplant recipients with HCV infection has been suggested to be considered only when the risk of not implementing treatment justifies the possible loss of the allograft, for example in patients with fibrosing cholestatic hepatitis or lifethreatening vasculitis. (KDIGO guidelines).

Death is high in those who have HCV infection. In our study it is statistically significant. Periera and coworkers compared the prevalence of post transplantation liver disease in HCV positive recipients. Those who have positive before transplantation, the

relative risk of liver disease was 5, graft loss was 1.3 and death was 3.3. There was increase in death resulting from sepsis with a relative risk of 9.9.[25]

Hepatitis B virus:

The prevalence of Hepatitis B infection in renal transplant recipients -3.9%. Santos et al his previous studies showed 6.2% and recent studies shows 2.6%[73]. Tsai etal[74] in his study prevalance was 9.2% .Concomitant hepatitis B and hepatitis C was 1%. Rejection rate -31.2%. Santos et al[73] his studies shows 0.7%. Santos et al his study rejection rate 46.4%

Mean duration after transplantation hepatitis B activation in our study is 13$\pm$2 months. Degos et al[77] mean duration of hepatitis B activation is 3-12 months.

Lamivudine resistance was 3/5 (60%) in our study. Thabut et al[75] shows lamivudine resistance is 57%. Kamar et al in his study lamivudine resistance in renal transplant recipients is 67%[74]. So In KTR recipients first itself start on entecavir to reduce the genetic barrier for resistance and nephrotoxicity[78]. In our study enzyme elevation with jaundice in 31.5% of patients. Su Kil Park et al[76] in his study 7 out of 14 (50%) of patients shows either clinical and biochemical manifestation of hepatic dysfunction. Mathurin et al[79] showed that in a cohort of 128 renal transplant recipients infected with HBV the 10 year survival was 55% compared with 80% in non hepatitis B infected renal transplant recipients. In our study Death rate was 18%.

Herpes Zoster infection:

Prevalence of herpes zoster infection in our study - 8.7%. Other studies recorded a prevalence of 3-10%[34,80]. In our cohort males are - 82%. Normally female gender is the risk factor for developing herpes zoster in liver transplant recipients not confirmed in renal transplant recipients. Median time of onset of herpes zoster is 9 month in our study. Previous studies between 3 and 92 months after transplantation.[81]

Disseminated with visceral involvement in only one case (3.4%). T.Arnes et al[84] 8.1% with visceral involvement with encephalitis and pneumonia..Mustapic et al[82] in his study also 2/37 had post herpetic neuralgia. In our study, 2/29 patients had post herpetic neuralgia. Recurrence occurs in 6.8%. Webster et al [83] in his studies second episode of herpes zoster in 5-15% of transplants.

In single dermatomal common region involved is throax followed by lumbosacral region. T Arnes et al[84] in his study throax 29.7% involved and followed by lumbosacral (16.7%).

We did not get statistically significant association between anti rejection therapy and varicella zoster. But CMV infection is a risk factor for developing herpes zoster. But in multidermatomal herpes zoster antirejection therapy comes as a significant risk factor. Arness etal[84] in his study also anti rejection therapy was not come as a significant risk factor. In our study graft dysfunction is not associated with herpes zoster but herpes zoster is the significant risk factor associated with patient survival.

Chicken pox infection:

Prevalence of chicken pox in our study - 3%. Most of the studies around 1-2%[85] Time of occurrence - 50% occurrence in < 6 months. One study 40% of case occur less than 6 months.[86]

Localized lesions in 54.5% patients. But Anupama kaul stated that 65.2% had localized disease.[85] In our study either Anti rejection therapy or NODAT are not come as a risk factor for chicken pox.

Death rate was 18.8%. Anupama kaul etal[85] his study 13.3% due to associated CNS infection and secondary bacterial infection. In our study also these 2 patients had encephalitis and superadded bacterial infection. Persistent graft dysfunction occurs in 18.18% of patients. Anupamaetal[85] in his study 29.8% had graft dysfunction after chickenpox .

Herpes simplex infection:

Prevealence of herpes simplex infection in our study 6%. Smith et al his prevalence20%[87]

Time of their presentation- mostly within 3 months. in our study 6 month $\pm$ 2 months. Only one case of encephalitis reported in our study. HSV is the most common cause of encephalitis in transplant recipients. One case of esophageal ulcer documented in our study. HSV esophagitis can cause dysphagia and may occur if the mucosa of an infected individual has been traumatized by nasogastric tube or endotracheal intubation.[87] Death occurred in 2 patients in our study. One patient had encephalitis and one patient had severe pneumonia. A small subset of patients (3.5%) has acyclovir resistant herpes simplex infection.[36]

HHV6 Infection:

Only one case reported. This patient had CMV infection also. This patient presented with rash.

HHV 6 virus causes exanthema subitum and HHV7 causes similar type of rash, leucopenia with lymphocytosis and spleenomegaly. Reactivation occurs in 60% of patients. It is possible CMV disease like symptoms with rash but negative for CMV may be attributable to HHV 6 infection[87]. Studies shows that CMV infection either precipitate or activated by HHV6 infection[88].

Ebstein barr virus infection:

In our study 2 patients had post transplant lymphoproliferative disorder due to ebstein barr virus infection. One patient presented as a graft dysfunction and lymphadnopathy and hepatomegaly Graft biopsy shows sheets of lymphocytes infiltrated into the interstitium. Another patient presented in one and half year after transplantation with chest discomfort and CT chest shows mutiple pulmonary nodule and hilar lymphadenopathy and cervical lymphadenopathy and graft dysfunction we didn't do graft biopsy for that patient. But we did lymph node biopsy and bone marrow aspiration and PET scan was done and it is proved to be Post transplant lymphoproliferative disorder. But treatment not yet started and lost follow up. Prevalence in our study was 0.5%. In kidney transplant recipients 1-2%[89]. PTLD is occur within one year of transplantation and is more common iin children[91]. Immunosuppresive drugs may produce activation and prolieration of EBV virus among B lymphocytes increase the chance of developing PTLD[90]. Recently PTLD incidence less

because use of lower immunosuppressive drugs and use of induction agents IL2 receptor antagonists and use of prophylactic vanganciclovir prophylaxis[3].

Parvo virus infection:

In our study 3 patients have parvo virus infection. Prevalence was 0.8%. On the basis of several studies the prevalence between 1-12%[92] . Two patients were presenting as a pure red cell aplasia one in 4th month and another patient in 9th month after transplant. Normally Onset of B 19 associated anemia has reported from 2 weeks to 63 months after transplantation[93.] Our patient does not have any typical of arthritis or rash and bone marrow aspiration shows pure red cell aplasia. Quantitative DNA PCR was positive. One patient was presented with graft dysfunction and protienuria and biopsy shows collapsing glomerulopathy and qualitative PCR for Parvo was positive.

Moudgil et al[94] reported the link between collapsing glomerulopathy and parvovirus.

Adeno virus infection:

Prevalence of adenovirus infection - 0.8% in our study. Mean time of onset occurs within 6 months of transplantation[95]. Our study also correlates this statement. Most frequently reported clinical syndrome has been hemorrhagic cystitis due to adenovirus type 11.[96] Our patients are also present with hematuria. One patient had graft loss and other two patients had persistent and progressive graft dysfunction. One patient was suspected to be acute cellular rejection and treated with antirejection therapy but serum creatinine not touched the baseline. Adenovirus can also present as a pyelonephritis.[97]

Human Papilloma virus infection:

Total number of patients -7 all are present with cutaneous warts.

Prevalence-1.95%. Cutaneous warts and precancerous lesions normally 15% at the time of transplantation and increased to 80% after 20 years, Sun exposed areas the face, neck, arm involved more commonly[98] Rudlinger et al. in his study (48%) were found to have warts, (11%) keratosis and (5%) to have, or recently to have had cancers. The longer the time of immunosuppression, the greater the prevalence of warts; Of those patients who had had their transplant for at least 5 years, 87% had warts. (10%) of 50 women had genital warts, four of them had internal lesions (vaginal, cervical or anal) and one developed a carcinoma of the vulva.

HIV Virus :

Only one patient had HIV ELISA is positive. He didn't have any history of sexual promiscuity or IV drug abuse. His CD4 count 300 cells/cu mm. Patient had HIV ELISA negative before transplant. He had no episode of rejection. Roland etal [99] survival rate for the patient (92%) and graft (85%) in 10 months were comparable to HIV negative patient rates.

Conclusion:

1. Bacterial, viral, fungal and parasitic infection contributes to 45%, 30.5%, 9.5%, 5.3% respectively to the total infective episodes.
2. Most of the viral episodes occurred after 6 months post transplant.
3. Commonest viral infection is the CMV and its prevalence 17.4% and mean time of onset is between 1-6 months after transplantation.
4. On Univariate analysis, antirejection therapy and NODAT had statistical significant risk factor for developing viral infection ($P<0.05$)
5. In patients affected with viral infection on univariate analysis, there is a statistical significance for graft dysfunction, graft loss and death ($p<0.05$)
6. CMV infection has a statistical significant risk factor for bacterial, fungal and other viral infections. ($p<0.05$)
7. Hepatitis C infection is the second most commonest virus found in our study, mean onset of infection is seen 6 months after transplant. Nearly 50% HCV infected patients developed NODAT.
8. Lamivudine resistance is more common in post transplant situation because prolonged treatment is necessary.
9. All the three patients with BK virus infection had persistent graft dysfunction.
10. Multi dermatomal involvement is commonly seen in our patients with herpes zoster(56%).

BIBLIOGRAPHY

1. Nina E. Tolkoff-Rubin and Robert H. Rubin-infection in Renal transplant recipients- Massory & Glassock Text book of Nephrology.
2. Joy A. Fishman MD infection in Renal transplant Recipients : Semin Neph vol. 27, No4, Jul. 2007 445-461.
3. Camille N. Kotton and Jay A. Fishman viral infection in the Renal transplant recipient. JASN 16:1758-1774, 2005.
4. Rubin RH: The direct and indirect effects of infection in liver transplantation: curr clin TopInfec Dis 22:125-154,2002.
5. Mitchell BM, Bloom DC, Cohrs Herpes simplex virus-1 and varicella zoster virus latency in ganglia. J Neurovirol 9:194-204, 2003.
6. Karras A, Thervet E:hemophagocytic syndrome in renal transplant recipients: Transplant 77;238-243.
7. Zhang Z, Kim SJ etal TNF receptor independent activation of CMV ; Transplantation 2008 : 85 (7) 1033-45.
8. Chapenko S , Folkmane I : Coinfection of two beta herpesviruses as an increased risk factor for CMV disease Clin Transplant14:486-492, 2000.
9. Rubin RH ,The indirect effects of CMV infection on the outcome of organ transplantation JAMA 1989:261:3607-3609.
10. Kalli AC, Levitsky J Meta analysis. The efficacy of strategies to prevent organ disease by CMV in solid organ Transplant Ann intern Med 2005:143:87 - 90.
11. Asberg A, Humar A et al Oral ganciclovir is non inferior to IV ganciclovir for treatment of CMV. Am J Trans 2007 : 7 (9) 2106 -13.

12. Kristel De Keyzer , Stenven Human CMV and kidney transplantation Am J Kid dis 2011:58(1)118-126.
13. Benvoisisn C, Weekers L, Xhignesse P Polyoma virus in Renal Transplantion Transplantation 2008: 85;S42-48.
14. Dugan AS, Eash S Update on BK virus –entry and intracellular trafficking . Trans inf Dis 2006;8:62.
15. Randhawa P, Brennan DC Bk virus infection in transplant recipients Am J trans 2006:6:2000-2005.
16. Ramos E , Drachenberg CB, Papadimitriou :clinical course of polyoma nephropathy JASN 2002:13:2145-2151.
17. Randhawa P, Ho A, Shapiro; Correlates of quantitative measurement of BK polyoma virus DNA with clinical couse of BKV infn in renal transplant recipients J clin micro 42:1176-1180, 2004.
18. Ding R, Medeiros M, Dadhania :Non invasive diagnosis of Bk virus nephritis by measurement of messenger RNA for BK virus Transplant 74 987-994, 2002.
19. Drachenberg CB, Hirsch HH Polyoma virus in renal transplantation ;Human Pathol2005;36;1245-1255.
20. Nina babel , Hans –Dieter Volk BK Polyomavirus infection and nephropathy: Nature review nephro 7 399-406 (2011).
21. M. Medeiros, J. Alberú, Polyoma virus in transplant recipients*Nefrología* 2008; 28 **(2)** 203-211.
22. Randhawa Ps , Anti BK virus activity of ciprofloxacin and related antibiotics Clin Infec Dis 2005;41:1366.

23. Orloff SL, stempel CA, :long term outcome in kidney in kidney transplant patients with hepatitis c infection Clin Transplant 9:119,1995.

24. Lee Wc, Shu KH: longterm impact of hepatitis B and c virus infection on renal transplantation Am J Neph 21:300:2001.

25. Periera BJ , wright TL The impact of pretransplantation hep C on outcome of renal transplantation Transplant 63:997,1997.

26. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ: Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 3: 178–185, 2003.

27. Bloom RD, Rao v Association of hepatitis c with post transplant diabetes in renal transplant patients on Tacrolimus JASN 13:1374, 2002.

28. Beddhu S, Bastacky S, Johnson JP: The clinical and morphologic spectrum of renal cryoglobulinemia. *Medicine1 (Baltimore)* 81: 398–409, 2002.

29. Magnone M, Holley JL, Shapiro R, Scantlebury V, McCauleyJ, Jordan M, Vivas C, Starzl T, Johnson JP: Interferonalpha- induced acute renal allograft rejection. *Transplantation* 59: 1068–1070, 1995.

30. Fabrizi, F., Martin, P., Dixit, V., Kanwal, F. &Dulai, G. HBsAg seropositive status and survival after renal transplantation: meta-analysis of observational studies. *Am. J. Transplant.* 5, 2913–2921 (2005).

31. Farza, H. *et al.* Hepatitis B surface antigen gene expression is regulated by sex steroids and glucocorticoids in transgenic mice. *Proc. Natl Acad. Sci. USA* 84, 1187–1191 (1987).

32. Krishna Moorthy, John GT profile of hepatitis B &C viruses in patients on dialysisand after transplantation unpublished data form CMC Vellore.

33. Patel R, Paya C : Infections in solid organ transplant patients Clin Microbiol Rev 10:86-124, 1997.

34. S. Gourishankar, J. C. McDermid, G. S. Jhangri, and J. K.Preiksaitis, "Herpes zoster infection following solid organ transplantation: incidence, risk factors and outcomes in the current immunosuppressive era," *American Journal of Transplantation*, vol. 4, No. 1, pp. 108–115, 2004.

35. A. Al Midani, J. Pinney, N. Field, C. Atkinson, T. Haque, andM. Harber, "Fulminant hepatitis following primary herpes simplex virus infection," *Saudi Journal of Kidney Diseases and Transplantation*, vol. 22, no. 1, pp. 107–111, 2011.

36. C. Danve-Szatanek, M. Aymard, D. Thouvenot et al., "Surveillance network for herpes simplex virus resistance to antiviral drugs: 3-year follow-up," *Journal of Clinical Microbiology*, vol. 42, no. 1, pp. 242–249, 2004.

37. Dborska D, Durlik M Human herpes virus-6 in renal transplant recipients .Transproce 35:2199-2201, 2003.

38. S. Jalilvand, Z. Shoja, T. Mokhtari-Azad, R. Nategh, and A. Gharehbaghian, "Seroprevalence of Human herpesvirus 8 (HHV-8) and incidence of Kaposi's sarcoma in Iran," *Infectious Agents and Cancer*, Vol. 6, No. 1, article 5, 2011.

39. Paya C, Fung JJ , Nalesnik MA, et al: Ebstein barr virus induced Post transplant lymphoproliferative disorder Transplant 68;1517,1999.

40. Rowe DT, Webber S, EBV virus load monitoring ; Its role in the prevention and management of PTLD ;Transplant Infec Dis 3:79, 2001.

41. Haque T, Wilkie GM : Treatment of EBV positive PTLD Lancet 360:436, 2002.

42. Brown KE, Anderson SM, Young NS: Erythrocyte P antigen Cellular receptor for B19 parvovirus. *Science* 262: 114–117, 1993.

43. Munakata Y, Saito-Ito T, Kumura-Ishii K, Huang J, Kodera T, Ishii T, Hirabayashi Y, Koyanagi Y, Sasaki T: Ku80 autoantigen as a cellular coreceptor for Human Parvovirus B19 infection. *Blood* 106: 3449–3456, 2005.

44. Moudgil A, Nast CC, Bagga A, Wei L, Nurmamet A, Cohen AH, Jordan SC, Toyoda M: Association of parvovirus B19 infection with idiopathic collapsing glomerulopathy. *Kidney Int* 59: 2126–2133, 2001.

45. Wong TY, Chan PK, Leung CB, Szeto CC, Tam JS, Li PK: Parvovirus B19 infection causing red cell aplasia in renal transplantation on tacrolimus. *Am J Kidney Dis* 34: 1132– 1136, 1999.

46. Hofland CA, Eron LJ, Washecka RM. Hemorrhagic Adenovirus Cystitis.
after Renal Transplantation. *Transplant Proc* 2004; 36: 3025–3027.

47. Deepali Kumar -AST hand book of transplant infections.

48. Sanjay Bhagnani etal –guidelines for kidney transplantation with HIV Infection Endorsed by British Transplantation Society

49. Dharnidharka VR , Agodoa Ly Risk factors for hospitalization for bacterial and viral infection in renal transplant recipients Am J trans 2007; 7; 653-61.

50. Stratta R. international congress on immunosuppression Orlando FL 1998.

51. Kanter J, PallardoL CMV infection in renal transplant recipients: Risk factors and Outcome. Transplant proc 2009 Jul-aug 2156-8

52. Green M, Avery R. Guidelines for prevention and Management of Infectious Complication Am J trans (suppl 10) 10-17 57-109, 160-163.

53. Helantera I, kyllonen primary CMV infection are common in kidney transplant recipients Am J transplant 2010 Sep. 10(9) 2026-32.
54. Arthurs SK, Eid AJ . Delayed onset primary cytomegalovirus disease and risk of allograft failure Clin infec dis 2008: 46 ; 840 - 846.
55. Eid Aj Bakri SJ clinical features and outcome of CMV retinitis after transplantation Trans Infec dis 2008:10:13-18.
56. Bratynska M, banasik M influence of cytomegalovirus disease on early and late allograft function. Transplant proceed 2006:38;147-150
57. S.Sagedel, K.P Nordal The impact of cytomegalovirus infection and disease on rejection episodes in renal allograft recipients Am J Tra vol2 no 9 850-856 2002
58. Limaye AP, Bakthavatchalam impact of CMV in organ transplant recipient in the era of antiviral prophylaxis Transplan 2006:81:1645-52
59. Jovana Cukaranovic, Sladjana Ugrenovic et al ,viral infection in renal transplant recipients scientific world journal Vol 2012 article ID 820621.
60. Ahuja M , Cohen Ep Polyoma virus infection at renal transplantation Transplantation 71:896-899, 2001.
61. Aaron Dall and Sundaran Hariharan Bk virus nephrits after renal transplantation CJASN 3:S68-S75 2008.
62. . Gupta M, Miller F, Nord EP, Wadhwa NK: Delayed renal allograft dysfunction and cystitis associated with human polyomavirus (BK) infection in a renal transplant recipient: A case report and review of literature. Clin Nephrol 60: 405–414, 2003. [PubMed: 14690258].

63. Howell DN, smith SR Diagnosis and management of BK polyoma interstitial nephrits in renal transplant recipients Transplantation 1999:68:1279-88.

64. Nickeleit V, Hirsch HH Polyoma virus infection of renal allograft recipients JASN 1999;10:1089-1090.

65. Vosnides GG. Hepatitis C in renal transplantation. *Kidney Int* 52:843-861, 1997.

66. .Roth D, Zucker K, Cirocco R, De Mattos A, Burke FW, Nery J, Esquenazi V, Babischkin S, Miller J: The impact of hepatitis C virus infection on renal allograft recipients. *Kidney Int* 45:238-244, 1994.

67. . Fabrizi F, Lunghi G, Marai P, Marcelli D, Guarnori I, Raffaele L, ErbaG, Pagano A, Locatelli F: Virological and histological features of hepatitis C virus (HCV) infection in kidney transplant recipients. *Nephrol Dial Transplant* 11:159-164, 1996.

68. Rostaing L, Izopet J, Cisterne JM, Arnaud C, Duffaut M, Rumeau JL, Puel J, Durand D : Impact of hepatitis C virus duration and hepatitis C virus genotypes on renal transplant patients: Correlation with clinicopathological features. *Transplantation* 65: 930–936, 1998.

69. Zylberberg H, Nalpas B, Carnot F, Skhiri H, Fontaine H, Legendre C, Kreis H, Brechot C, Pol S: Severe evolution of chronic hepatitis C in renal transplantation: A case control study. *Nephrol Dial Transplant* 17: 129–133, 2002

70. Cosio FG, Pesavento TE, Osei K, Henry ML, Ferguson RM: Post-transplant diabetes mellitus: Increasing incidence in renal allograft recipients transplanted in recent years. *Kidney Int* 59: 732–737, 2001.

71. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Kanwal F, Dulai G: Post-transplant diabetes mellitus and HCV seropositive status after renal transplantation: Meta-analysis of clinical studies. *Am J Transplant* 5: 2433–2440, 2005.

72. Jose Maria Morales , Roberto Marcen renal transplantation in patients with hepatitis C virus antibody. NDT 2010 3 (supl2)41-46.

73. Santos L R Alves : impact of hepatitis B and c virus infection after renal transplantation Transplant proceding 41 880-882

74. Kamar N, Sandres-Saune K, Ribes D, Duffaut M, Selves J, Durand D, Izopet J, Rostaing L. Effects of long-term lamivudine therapy in renal-transplant patients. *J Clin Virol* 2004;31: 298-303

75. Thabut D, Thibault V, Bernard-Chabert B, Mouquet C, Di Martino V, Le Calvez S, Opolon P, Benhamou Y, Bitker MO, Poynard T. Long-term therapy with lamivudine in renal transplant recipients with chronic hepatitis B. *Eur J Gastroenterol Hepatol* 2004; 16: 1367-1373

76. Su Kil Park , won seok yang outcome of renal transplantation in hep B positive patients NDT 2001 16 2222-2228

77. Degos F, Lugassy C, Degott C, Debure A, Carnot F, Theirs V, Tiollais P, Kreis H, Brechot C. Hepatitis B virus and hepatitis B-related viral infection in renal transplant recipients. A prospective study of 90 patients. *Gastroenterology* 1988; **94**:151-156

78. Ming chou Tsai,yen ta chan hepatitis B infection and renal transplantation, world journal of gastroenterology 2010 Aug 21 16(31) 3878-3887

79. Mathurin P, MouquetC, Poynard T impact of hepatitis B on kidney transplantation hepatology 29257 ; 1997.

80. Miller GG, Dummer JS: Herpes simplex and varicella zoster viruses: forgotten but not gone. Am J Transplant 2007; 7: 741–74773: 608–611.

81. Rodriguez-Moreno A, Sanchez-Fructuoso AI, Calvo N, Ridao N, Conesa J, Marques M, Prats D, Barrientos A: Varicella infection in adult renal allograft recipients: experience at one center. Transplant Proc 2006; 38: 2416–2418

82. Z. Mustapic a N. Basic-Jukic a Varicella Zoster Infection in Renal Transplant Recipients: Prevalence, Complications and Outcome Kidney Blood Press Res 2011;34:382–386

83. Webster A, Grint P titration of IgG antibodies against varicella zoster after transplantation is not predictive of future zoster J med viro 1989 27:117-119

84. T Arnes , R. Pederson Varicella zoster virus associated disease in adult kidney transplant recipients Transplan Infec dis 2008 10 260-26

85. Anupama kaul, Raj K Sharma chicken pox infection after renal transplant CKJ 2012 5 203-206

86. Parnhalm AP Flexman JP Primary varicella in adult renal transplant recipients clin trans 1995 ; 9;115-118

87. Smith SR , butterlyDW , viral infection after transplantation Am J Kid dis 2001 ;37; 659-676

88. Singh N , carrigan D : Human Herpes virus 6 in transplantation . An emerging pathogen Ann intern med 124: 1065-1071, 1996

89. TrofeJ , Buell JF Analysis of factors that influence survival with PTLD in renal transplant recipients AM J Trans 2005:5:775-780

90. Allen U, Peerikasitits J EBV and PTLD in solid organ transplant recipients Am J trans 2009(9)S87-S96

91. Marcelo Santos Sampaio Yong w cho Impact of EBV donor and recipient serostatus on incidence of PTLD NDT 2012 27:2971-2979

92. Ki CS, Kim IS, Kim JW, Lee NY, Kim SH, Lee KW, Kim SJ, Joh JW, Huh WS, Oh HY: Incidence and clinical significanceof human parvovirus B19 infection in kidney transplant recipients. *Clin Transplant* 19: 751–755, 2005

93. .Marchand S, Tchernia G, Hiesse C, Tertian G, Cartron J, Kriaa F, Boubenider S, Goupy C, Lecointe D, Charpentier Human parvovirus B19 infection in organ transplant recipients. *Clin Transplant* 13: 17–24, 1999

94. Moudgil A, Shidban H, Nast CC, Bagga A, Aswad S, Graham SL, Mendez R, Jordan SC: Parvovirus B19 infection- related complications in renal transplant recipients: Treatment with intravenous immunoglobulin. *Transplantation* 64: 1847–1850, 1997

95. Yagisawa T , Takahashi K , adenovirus induced nephropathy in kidney transplant recipients. Transpl proced 1989 ;21;2097-2099

96. Shindo K, Kitayama T acute hemorhhagic cystitis caused by adenovirus type 11 after renal transplantation Urol inter 1986;41 152-155

97. .KIM ss , Hicks j adenovirus pyelonephritis in apediatric renal transplant recipients Pediat nephrol 2003 May 18(5) 457-61.

98. Dreno B, Manstat E, skin cancers in transplant patients, NDT 1998:13(6) 1374-1379

99. Abbott Kc , Swanson SJ, HIV and kidney transplantation in the era of HAART therapy JASN 2004: 15:1633-1639.

100. V.Jha Post transplant infections: An ounce of prevention Indian journal of Nephrology oct 2010 vol20issue4 171

KEY TO MASTER CHART

DOT - date of transplant

F.U - follow up duration

Cr.f. - creatinine at follow up

Gd - graft dysfunction

G.s - graft survival

G.L - graft loss 1 - present 2 - graft lost

P.S - patient survival 2 - died

DA - donor age

Chi - chicken pox

H.Z - herpes zoster

Hes - herpes simplex

Ade - adeno

H6 - human herpes virus 6

Pro - parvo

EBV - ebstein barr virus

HPV - human papilloma virus

HCV - hepatitis B virus

TB - tuberculosis

1 - present

2 - absent

Fun - fungal

I.s - immunosuppressants

Cyclo/Aza - 1

Cyclo/MMF- 2

Tacro/MMF- 3

Tacro/aza - 4

PROFORMA

POST TRANSPLANT VIRAL INFECTION

Name Age Sex Date of transplant

NKD

Donor Age Sex

Pre transplant cmv status of donor Recipient

Pretransplant Hepatitis B prettransplant hepC Pretransplant any other

Hepatitis B vaccination Varicella vaccination

Pre transplant hepB treatment and viral load

Warm ischemic time Cold ischemic time

Immunosuppression Induction agent

Rejection CNI toxicity

Biopsy

HB Total wbc DC Platelets Periph smear

Retic count LDH coombs

Urine R/E urine c/s blood c/s

LFT T.Bil dire indirect OT PT ALP T.p alb glob

Blood sugar urea creatinine electrol

X ray chest

Viral markers HBs ag HIV HCV anti HAV anti HEV

CT Chest PET

Usg abdomen renal Doppler

CSF exam microbial | Prot | Serology

Pleural fluid | Ascitic Fluid

Upper gi endos | Colonos

BAL | Cytology | Culture

Bone marrow aspiration | Bonemarrow biopsy

Liver biopsy

Skin biosy

Tzanck smear:

Association of other bacterial / fungal infections - time | Culture

CMVinfection | Months after transplant

Cmv pp65 | CMV PCR | Repeat

Type of presentation-viral syndrome/retinitis/colitis/pneumonits /hepatitis /ulcer

Treatment status | Responsiveness

BK virus: | Months after transplant.

Urine for decoy cells | Quan PCR

Hepatitis C virus | Month aft trx

Quant pcr

Treatment | Responsiveness

Hepatitis b virus | Month after tx

Quanti PCR

Treatment | Responsiveness

Herpes zoster | Month after tx | Recurrence

Multidermato/single dermatome

Complication:encephalitis/post herpetic neuralgia/cut scarring

Treatment Responsiveness

Chicken pox: Month after TX

Complication

Treatment

Herpes simplex: Month after tx

Type of presentation

Treatment Responsiveness

EBV: Month after TX

Type of presentation:

Treatment Responsiveness

Other herpes viruses:

Type of presentation Treatment

Parvo virus: Month after tx

Qunat PCR

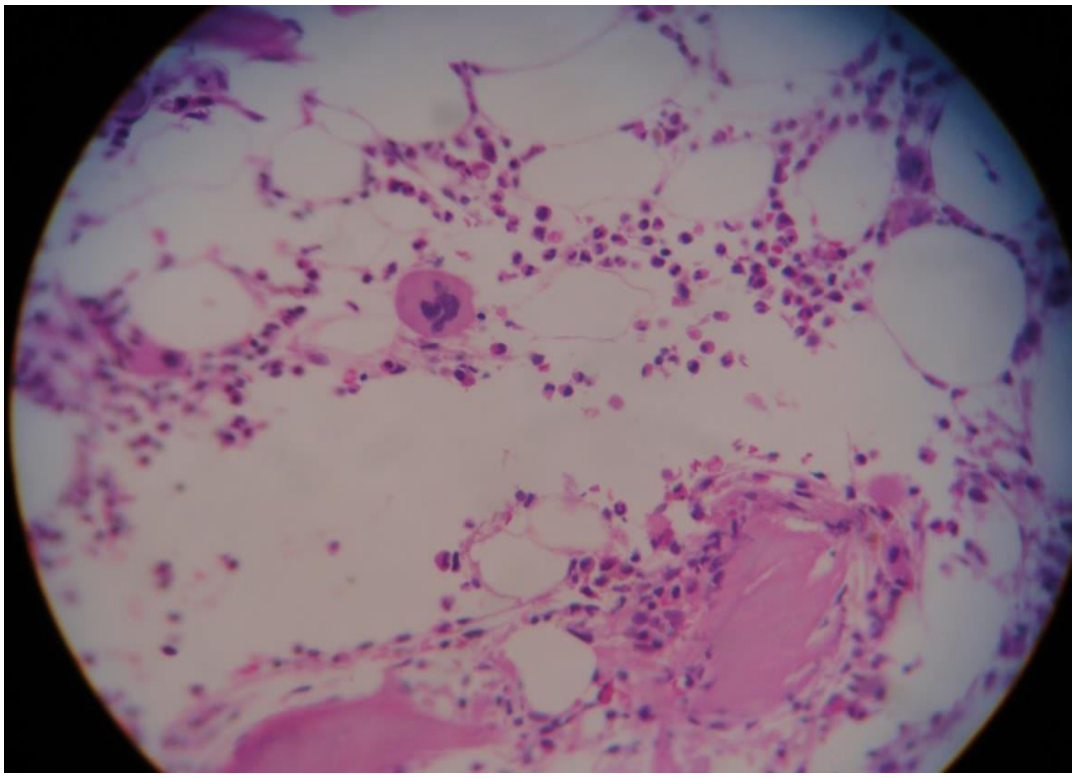
Adenovirus: Month after Tx

Type of presentation Treatment

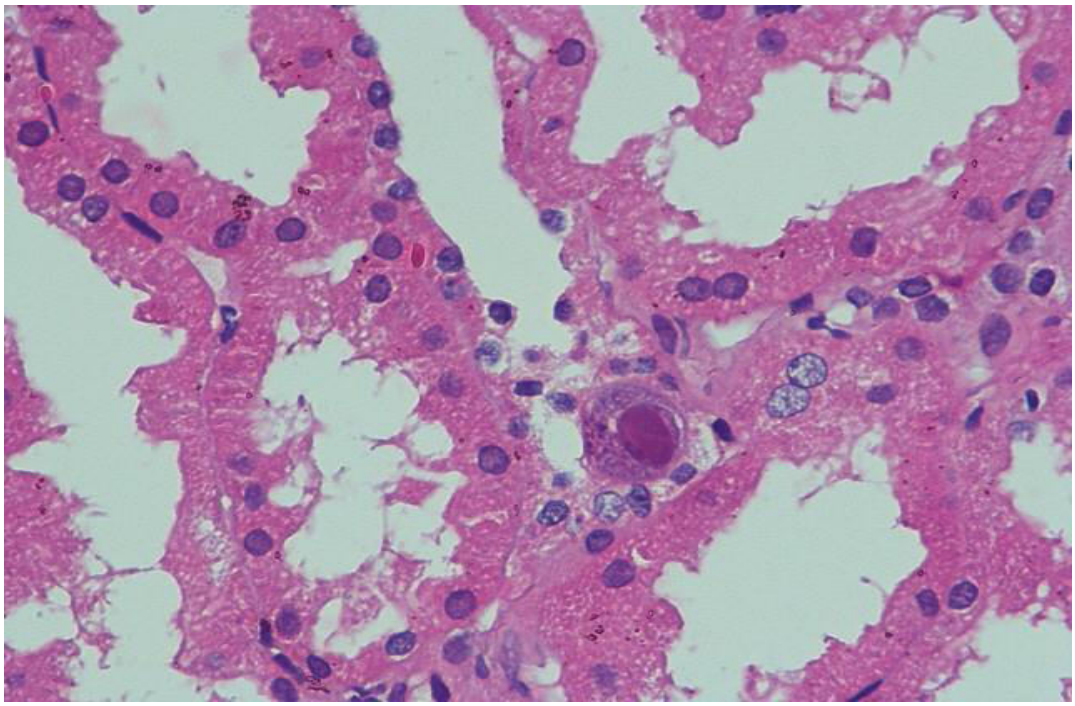
Human papilloma virus : Month after Tx

Type of presentation Treatment

Other viruses:

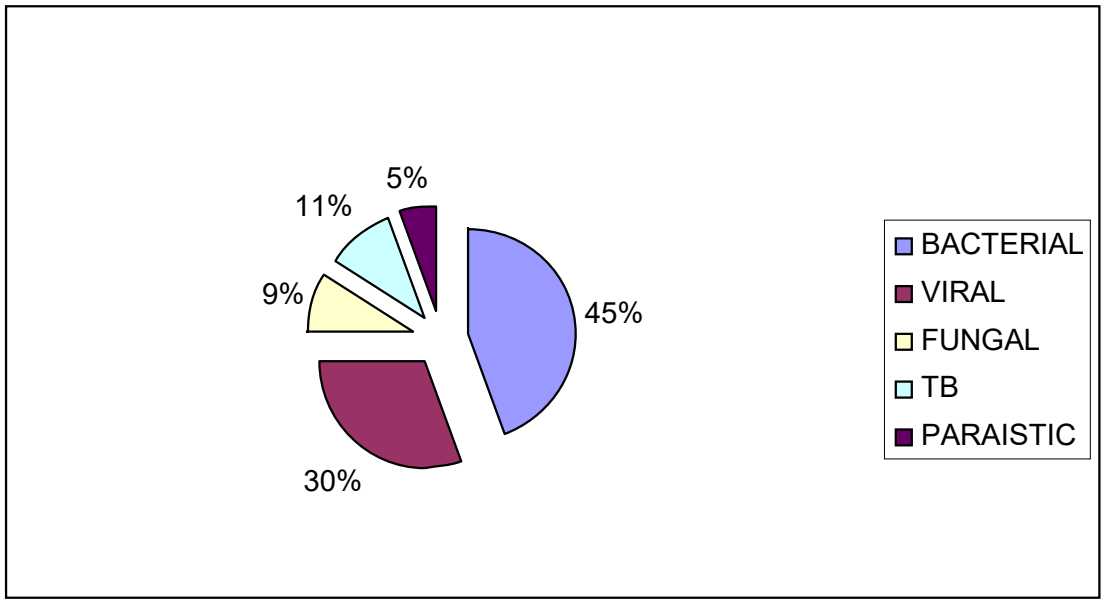


BoneMarrow Aspiration--Megakaryocytes adequate. myelopoiesis normal. Red cell precursors decreased - pure red cell aplasia (parvo virus induced)

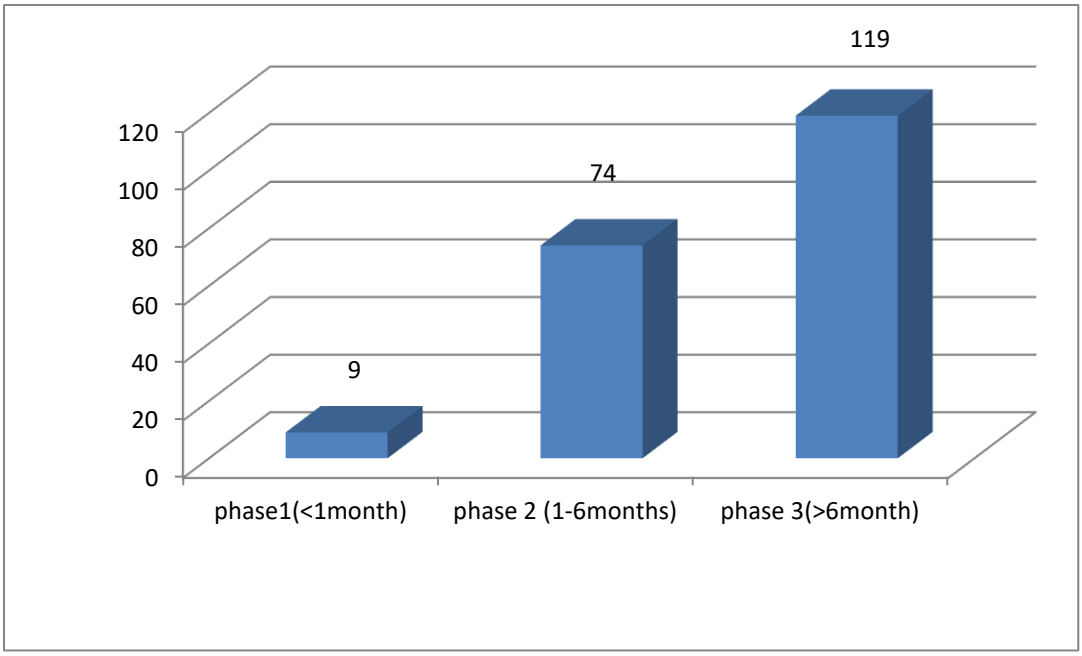


Allograft biopsy shows viral inclusion

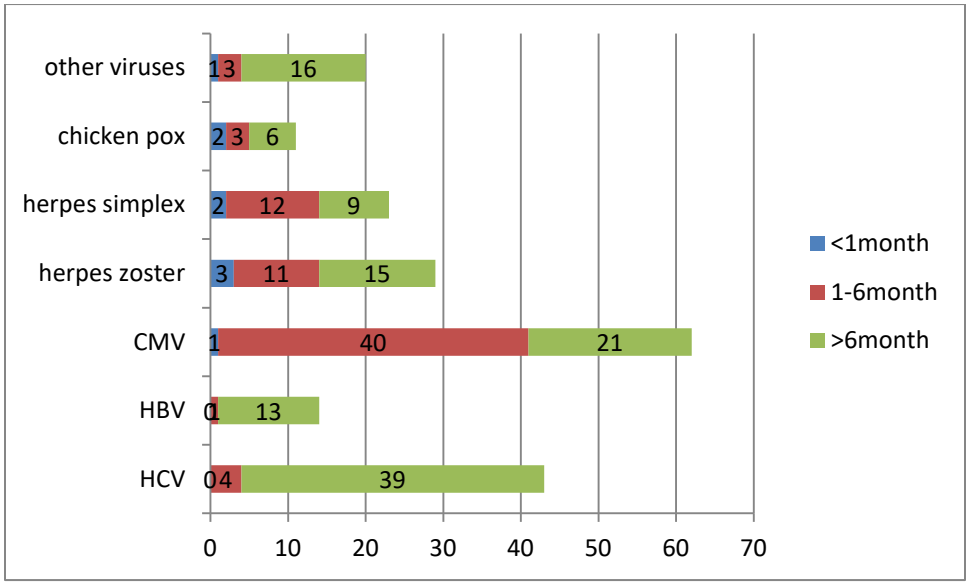
TOTAL INFECTIVE EPISODES



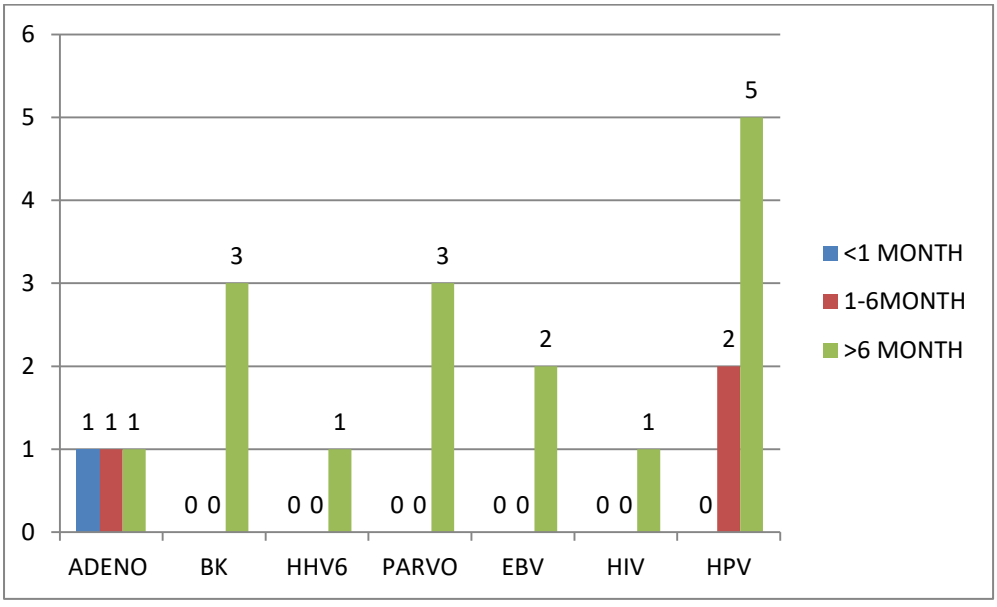
TIME OF OCCURRENCE OF VIRAL INFECTIVE EPISODES



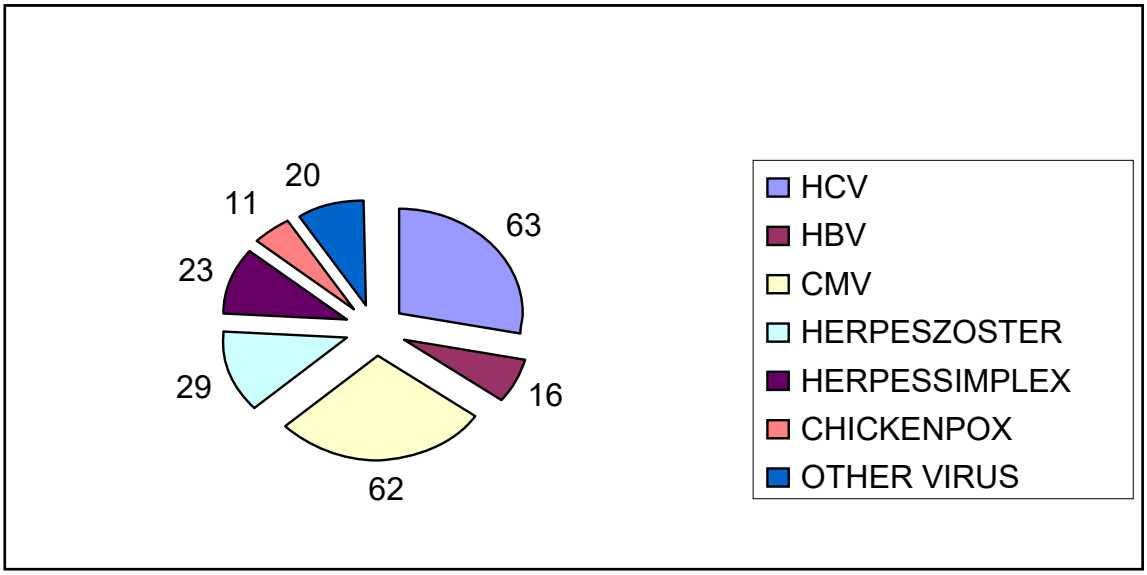
TIME OF OCCURRENCE OF DIFFERENT VIRAL INFECTION



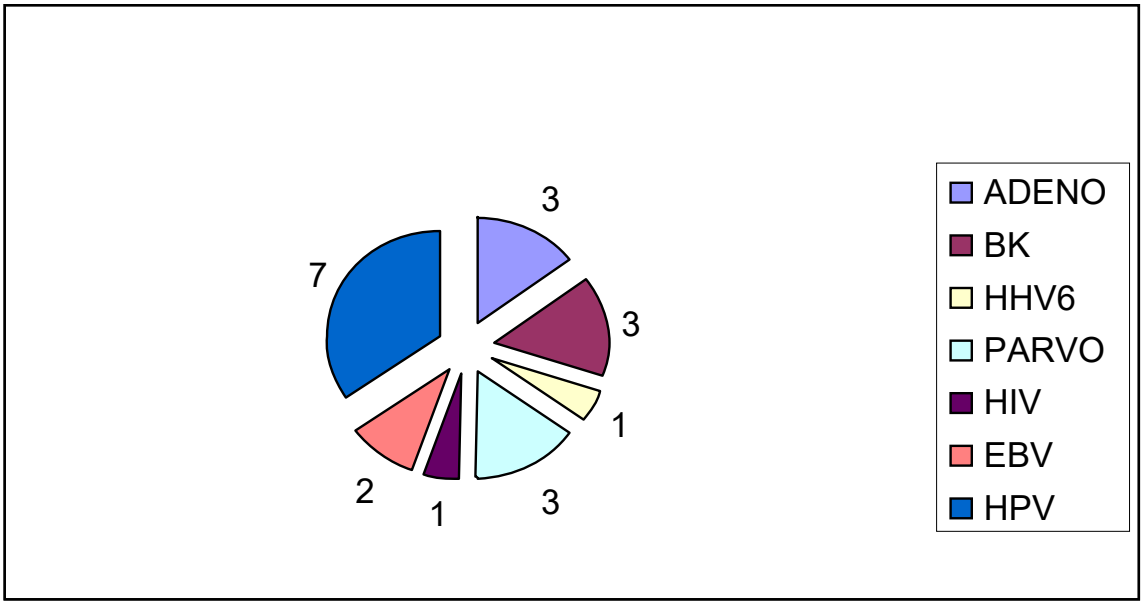
TIME OF OCCURRENCE OF OTHER VIRUSES



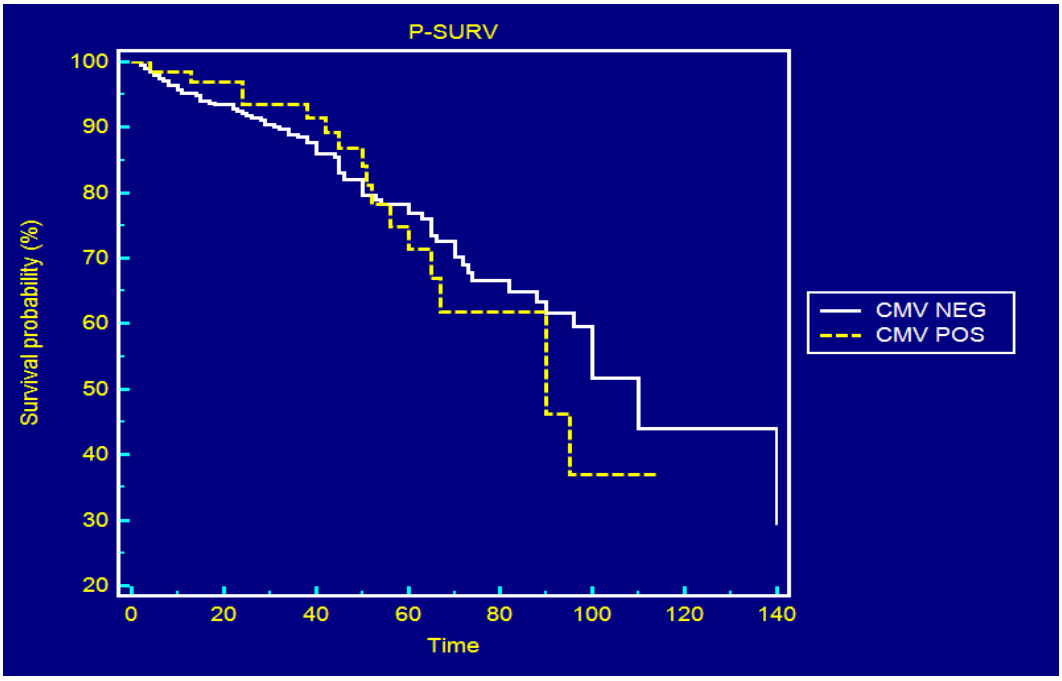
VIRAL INFECTIVE EPISODES



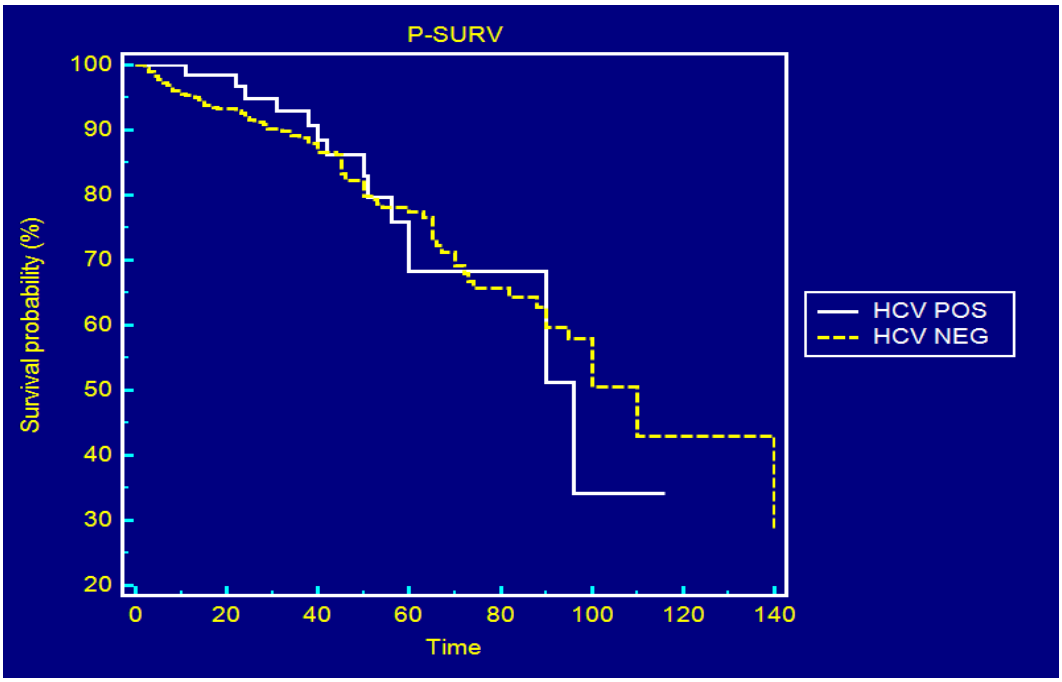
OTHER VIRUSES

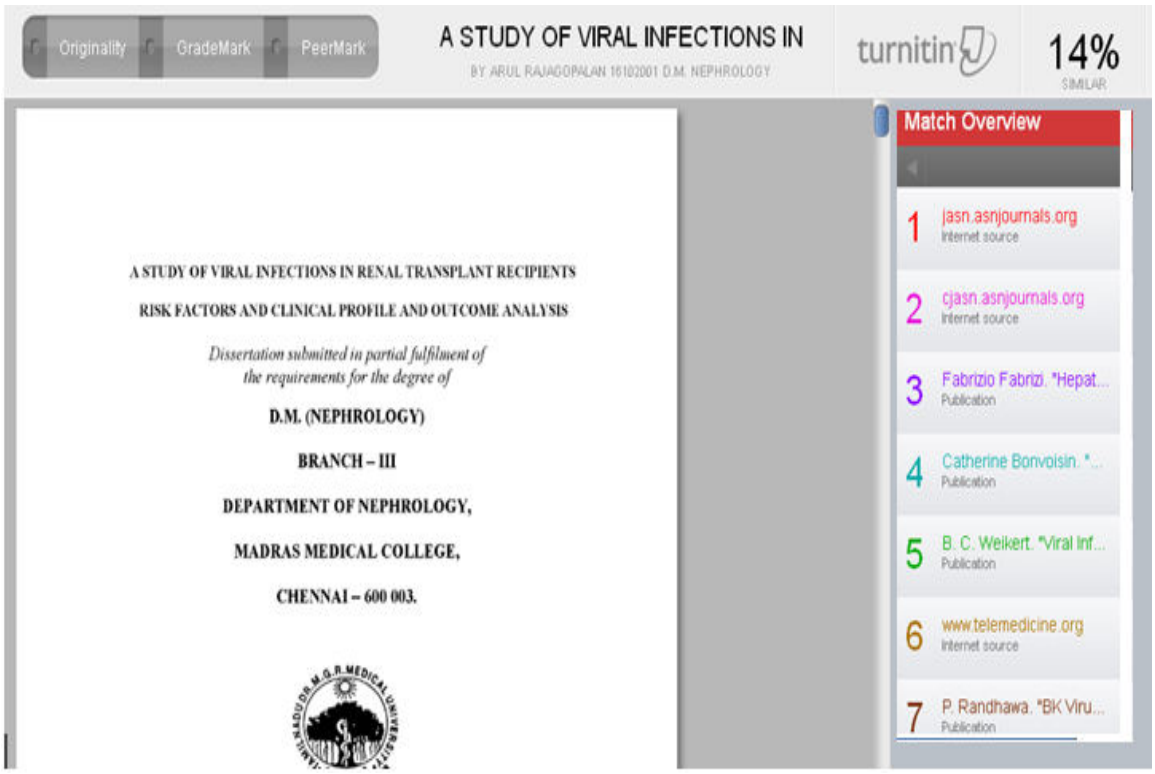


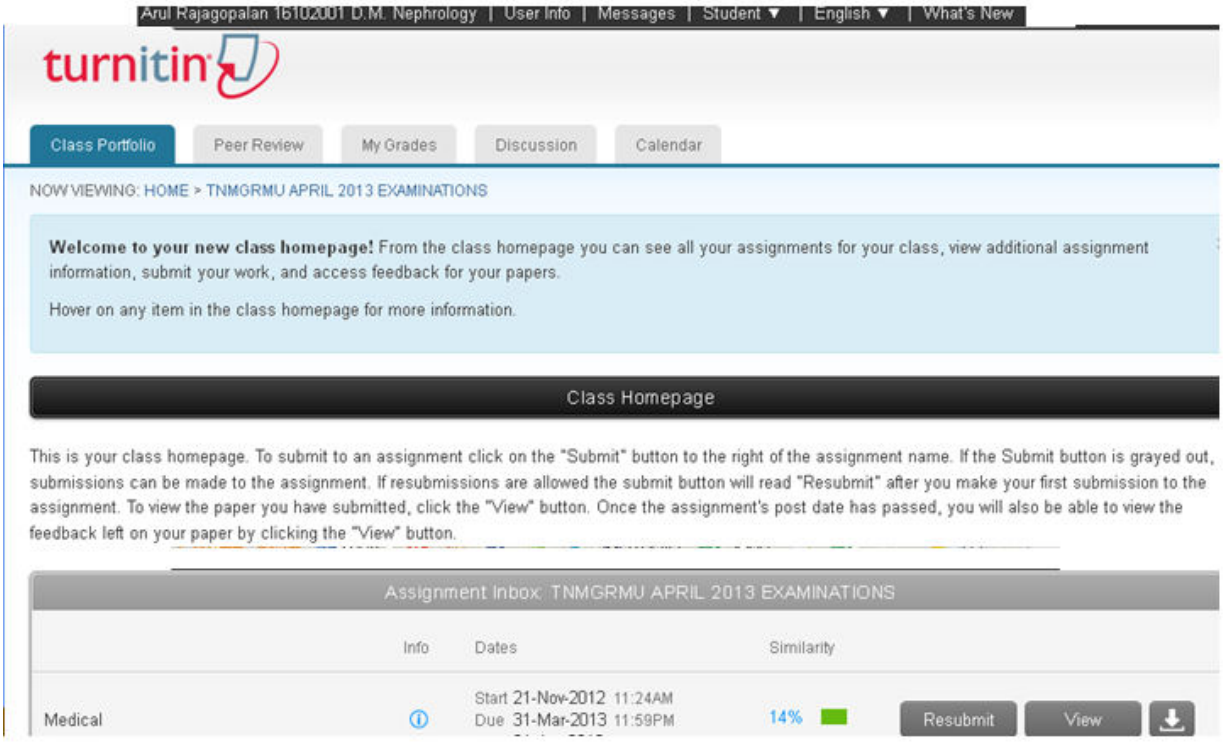
IMPACT OF CMV ON PATIENT SURVIVAL



IMPACT OF HCV ON PATIENT SURVIVAL




Originality
GradeMark
PeerMark
A STUDY OF VIRAL INFECTIONS IN
BY ARUL RAJAGOPALAN 16102001 D.M. NEPHROLOGY
turnitin
14%
SIMILAR
A STUDY OF VIRAL INFECTIONS IN RENAL TRANSPLANT RECIPIENTS
RISK FACTORS AND CLINICAL PROFILE AND OUTCOME ANALYSIS
Dissertation submitted in partial fulfilment of
the requirements for the degree of
D.M. (NEPHROLOGY)
BRANCH – III
DEPARTMENT OF NEPHROLOGY,
MADRAS MEDICAL COLLEGE,
CHENNAI – 600 003.
Match Overview
1 jasn.asnjournals.org Internet source
2 cjasn.asnjournals.org Internet source
3 Fabrizio Fabrizi. "Hepat... Publication
4 Catherine Bonvoisin. "... Publication
5 B. C. Welkert. "Viral Inf... Publication
6 www.telemedicine.org Internet source
7 P. Randhawa. "BK Viru... Publication


Arul Rajagopalan 16102001 D.M. Nephrology | User Info | Messages | Student ▼ | English ▼ | What's New
turnitin
Class Portfolio
Peer Review
My Grades
Discussion
Calendar
NOW VIEWING: HOME > TNMGRMU APRIL 2013 EXAMINATIONS
Welcome to your new class homepage! From the class homepage you can see all your assignments for your class, view additional assignment information, submit your work, and access feedback for your papers.
Hover on any item in the class homepage for more information.
Class Homepage
This is your class homepage. To submit to an assignment click on the "Submit" button to the right of the assignment name. If the Submit button is grayed out, submissions can be made to the assignment. If resubmissions are allowed the submit button will read "Resubmit" after you make your first submission to the assignment. To view the paper you have submitted, click the "View" button. Once the assignment's post date has passed, you will also be able to view the feedback left on your paper by clicking the "View" button.
Assignment Inbox: TNMGRMU APRIL 2013 EXAMINATIONS
Info
Dates
Similarity
Medical
Start 21-Nov-2012 11:24AM
Due 31-Mar-2013 11:59PM
14%
Resubmit
View

turnitin

Your digital receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

Paper ID	314027724
Paper title	A STUDY OF VIRAL INFECTIONS IN RENAL TRANSPLANT RECIPIENTS - RISK FACTORS CLINICAL PROFILE AND OUTCOME ANALYSIS
Assignment title	Medical
Author	Arul Rajagopalan 16102001 D.M. Nephrology
E-mail	arul752000@yahoo.co.in
Submission time	22-Mar-2013 10:51AM
Total words	9450

First 100 words of your submission

A STUDY OF VIRAL INFECTIONS IN RENAL TRANSPLANT RECIPIENTS RISK FACTORS AND CLINICAL PROFILE AND OUTCOME ANALYSIS Dissertation submitted in partial fulfilment of the requirements for the degree of D.M. (NEPHROLOGY) BRANCH – III DEPARTMENT OF NEPHROLOGY, MADRAS MEDICAL COLLEGE, CHENNAI – 600 003. THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY CHENNAI AUGUST 2013 AIMS AND OBJECTIVES 1. To study the clinical profile of viral infections in post renal transplant receipients 2. To study the risk facors and the effect of viral infections on graft outcome. Introduction Renal transplantation has become the most effective means of rehabilitating patients with end stage renal disease. In well established...